PROGNOSIS OF PULMONARY SARCOIDOSIS *

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MOST of what is known about the prognosis of pulmonary sarcoidosis has been gathered from studies in the last decade, where the outcome has varied remarkably (fig. 1). The crude figures for improvement and mortality show that only 29% of Siltzbach's (1955) patients were improved, compared with 83% of Löfgren's (1953): and 23% of Riley's (1950) patients died whereas Löfgren's (1953) had no mortality (fig. 2).

There are several reasons for these striking differences. In part they are probably racial. American reports (Sones et al. 1949, Riley 1950, Longcope and Freiman 1952, Siltzbach 1955, Sones and Israel 1960) include many Negroes, and Sones and Israel (1960) have recently confirmed the unfavourable outcome for the Negro, claiming that it is related to a greater frequency of cutaneous sarcoidosis rather than to other factors. Another reason for reported discrepancies is the stage of the disorder observed. Löfgren (1953) dealt mainly with early sarcoidosis; and Riley (1950), for example, with advanced or even terminal disease. Moreover, many of Löfgren's Swedish patients (111 of 201) were found to have hilar lymph-node enlargement at an attack of erythema nodosum, which is much commoner there than in this country or in North America. Because this form has a better prognosis than others, as Löfgren found, the favourable outcome for most of his patients applies to fewer elsewhere, as we have seen. One further qualification to some recent figures (Siltzbach 1955, Sones and Israel 1960) is that they have included many patients treated with corticosteroids. Another is that observation has not always been long enough for conclusions to be drawn about the evolution of the disease, which may take years or even decades. For these various reasons it has been difficult to get a perspective of the natural history which foreshadows what path the disorder may take or where it may lead the individual patient.

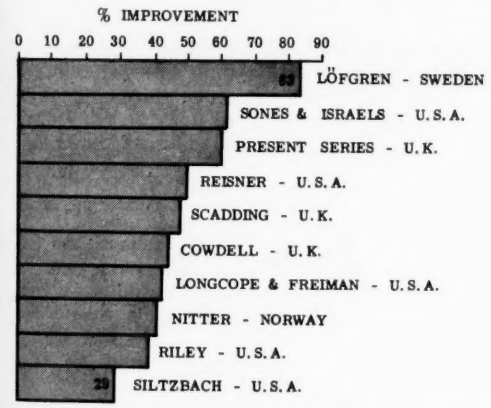

Fig. 1—Pulmonary sarcoidosis. Percentage improvement in the literature.

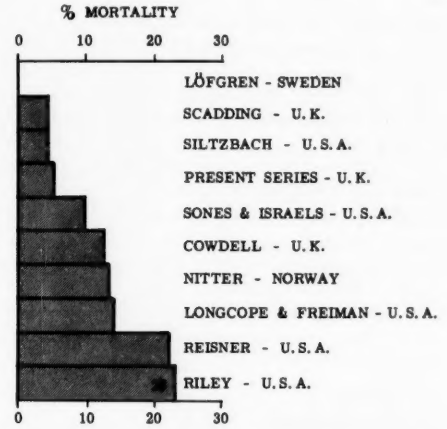

Fig. 2—Pulmonary sarcoidosis. Percentage mortality in the literature.

From our studies at King's we have been able to get a clearer view of the alternatives. It is based on observation of 125 patients for periods of two to twenty-two years—in half of them for more than four years (Smellie and Hoyle 1960). In following the natural history we depend upon radiography, especially in the early part when clinical abnormalities are minor or transient and cardiorespiratory function is little if at all disturbed. In making this choice we have to accept the limitations of radiography, for it is well known that a normal lung field may conceal histological sarcoidosis. However, events have shown that this does not lead to serious or frequent errors in judging the clinical course, though it accounts for some discrepancies where the diffusing capacity is defective in patients with a normal or near normal radiograph comparatively late in their disease.

Course of Illness

The initial radiographic composition of our series of patients is shown in table I. The main point here is that every stage of the disorder was represented at the time of recognition, even diffuse pulmonary fibrosis.

The ages of these lesions at the time of their discovery could be estimated at first only on rare occasions; but as the investigation progressed this handicap could be overcome, to some extent, in two ways. The first was by noting the time course of subsequent changes in the two main groups, one with hilar-node enlargement and the other with pulmonary infiltration; and the second was the observation that hilar-node enlargement was not seen to

TABLE I—INITIAL CHEST RADIOGRAPHS OF 125 PATIENTS

Enlarged hilar nodes only	48 (38%)
Pulmonary infiltration and enlarged hilar nodes	62 (50%)
Pulmonary infiltration only	9 (7%)
Pulmonary fibrosis	6 (5%)

*From the Marc Daniels lecture given at the Royal College of Physicians of London on Jan. 12, 1961.

occur after pulmonary infiltration but always preceded or accompanied it.

The radiographic course of the patients with enlarged hilar lymph-nodes only at the time of discovery is shown in table II. 7 others in this group were excluded because they were treated at some time for uveitis with impaired vision. In about two-thirds of the 41 untreated patients the enlarged nodes resolved completely within a mean time of a year from recognition, leaving normal radiographs and fit patients; and in none of them did the nodal enlargement recur.

A small group—about one-tenth—showed decreasing enlargement over several years but was usually left with recognisable nodes. In the rest, some 7%, the nodes remained much enlarged (figs. 3 and 4). There is evidence from necropsies that these nodes often became hyalinised after fibrous healing of the follicles (Smellie and Hoyle 1957). Patients with nodal enlargement only have remained well and at work, free from symptoms and from important functional defects. Although submucosal follicles in the bronchial tree are probably common in these patients they rarely give rise to symptoms; and bronchial stenosis, in our experience, is part of the progressive form of the disease when it occurs.

TABLE II—RADIOGRAPHIC COURSE OF 41 UNTREATED PATIENTS WITH HILAR-NODE SARCOIDOSIS FOLLOWED FOR TWO YEARS OR MORE

Radiography	Number of patients	Time of appearance	
		Mean	Range
Clear radiograph (via pulmonary infiltration in 8)	25 (61%)	10·3 mos.	2–31
Lesions regressing	4 (10%)		
Nodes unchanged	3 (7%)		
Infiltration increasing	6 (15%)		
Pulmonary fibrosis (2 dead)	3 (7%)	5·4 yr.	4–7
Total	41		

Pulmonary infiltration appeared in about one-fifth of the patients with nodal enlargement, usually within a year, rarely after two years. Fig. 5 shows the outcome of untreated pulmonary infiltration, whether found initially or following nodal enlargement. Some 41% of these patients achieved a normal radiograph. The mean time for this was about a year; in 17 of 22 it was within two years of recognition, and in the other 5 within three years. As with nodal enlargement, pulmonary infiltration has not recurred in any of these patients after complete spontaneous clearing, and it seems to be rare for it to do so.

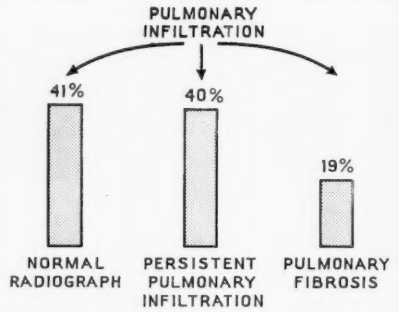

Fig. 5—Radiographic course of pulmonary infiltration.

Persistent pulmonary infiltration follows one of two distinct courses to which the prognosis is closely related. It remains virtually unchanged in about one-fifth—and in about half of the others there is increasing infiltration for a variable time, after which it remains unaltered. Figs. 6 and 7 show a typical example. Such patients, about 40% of all those with pulmonary infiltration, have so far failed to show gross lung destruction from fibrosis and have not become progressive respiratory invalids even after many years, though some are left with a residual defect in their diffusing capacity. They are well and at work in spite of their persistent lesions; and only 1 of 35 has died.

The remaining patients, some 19% of those with pulmonary infiltration (fig. 5), have deteriorated steadily. This progressive form of the disease accounts for almost all its serious features. It accounts for slowly advancing invalidism from lung failure, with dyspnœa the main symptom becoming important in about five years and coinciding roughly with recognition of fibrosis radiographically. Eventually this reaches the characteristic appearance seen in the example shown in figs. 8 and 9. This form of progressive sarcoidosis leads to severe symmetrical bronchiectasis, chiefly in the upper lobe (figs. 10 and 11) (6 in 125), with late secondary infection; and often to bullæ and occasionally to bronchostenosis (4 in 125) or to pneumothorax (5 in 125). Only 1 of the 125 patients, however, has developed caseous tuberculosis: it appeared late in the course of a progressively fibrosing sarcoidosis and she died from cor pulmonale fifteen years after the discovery of hilar lymph-node enlargement. Cor pulmonale (table III), the final complication, occurs from the end of the first decade. In 5 out of 6 in this series it was fatal within a year of the first bout of congestive cardiac

TABLE III—RELATION BETWEEN ONSET OF COR PULMONALE, DURATION OF DISEASE, AND TIME OF DEATH

Patient	Interval between onset of cardiac failure from cor pulmonale and death	Number of episodes of cardiac failure from cor pulmonale	Duration of sarcoidosis (years) before first episode of cardiac failure from cor pulmonale
A	9 months	3	21
B	10 months	2	3
C	2½ years	4	13
D	1 month	1	15
E	At time of death	1	10
F	6 months	2	9

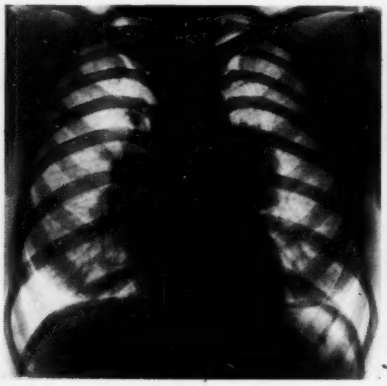

Fig. 3—Female, aged 38. Bilateral hilar lymph-node enlargement found 2 years previously by a routine chest radiograph. A liver biopsy showed epithelioid cell follicles.

Fig. 4—Same patient as fig. 3, taken 6 years later. The nodal enlargement, known to have been present for at least 8 years, persists almost unchanged.

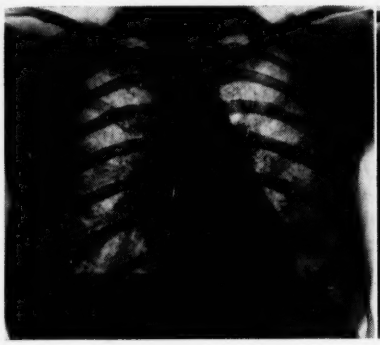

Fig. 6—Female, aged 29. Diffuse fine stippled shadows of pulmonary sarcoidosis (type II) found 2 years after an attack of erythema nodosum at mass radiography 4 years before this radiograph was taken. A liver biopsy showed epithelioid cell follicles at that time and again a year after this radiograph was taken.

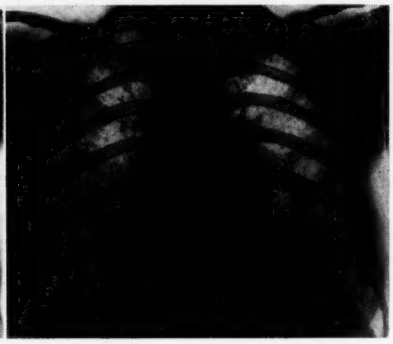

Fig. 7—Same patient as fig. 6. Radiograph taken 8 years after fig. 6. The fine stippled shadows, present for 12 years, are unchanged (type II).

failure. Half of our patients with progressive pulmonary sarcoidosis have died, though the mortality from sarcoidosis of the whole series of 125 is no more than 6% so far.

Three Types

From these main features of the natural history three types of pulmonary sarcoidosis can be recognised.

I. *Benign with Spontaneous Resolution*

Hilar-node enlargement may or may not be followed by transient pulmonary infiltration. A normal radiograph may be expected within about two years and there is no disability and no mortality. Some 51% of patients in this series have belonged to this group.

II. *Chronic but Non-progressive*

Hilar lymph-node enlargement may persist and pulmonary infiltration always persists; but the pulmonary lesions fail to increase progressively, so that eventual fibrosis is not severely destructive. Disability is usually slight; the prognosis is good in spite of lasting radiographic changes; and the mortality is low. 36% of patients in the present series come into this category, though it is yet too soon to say whether the ultimate fate of some of them may not be that of type III.

III. *Chronic and Progressive*

The lungs are infiltrated by follicles for many years, lung destruction and fibrosis are cumulative and severe, respiratory disability steadily increases, and the eventual mortality is high. About 13% of patients in this series have so far been found to have disease which has taken this progressive course. The early stages here are very deceptive, but as sarcoidosis is commonest in young adults few patients with this form are likely to survive beyond middle life without treatment; and the few who do survive will be disabled.

Activity of Sarcoid Process

These striking differences in the course and outcome of pulmonary sarcoidosis are consistent with the view that they depend chiefly upon the time for which the sarcoid process remains active in the individual host and is operative in the lung. At present we are completely in the dark about the factors which control this situation, though there is some clinical evidence from which it is sometimes possible to foretell when they are likely to operate for a limited or for a long time. The first, as Löfgren (1953) showed, is that the active course is usually short when sarcoidosis is ushered in by an attack of erythema nodosum; and we have confirmed this. Moreover, the prognosis is good when nodal enlargement only is found initially and pulmonary infiltration does not appear within the next year. There is a trend towards a better prognosis when pulmonary infiltration is symptomless at the onset and when it is finely nodular. The

Fig. 10—Same patient as figs. 8 and 9. Bronchogram taken a year before death and 9 years after an attack of iritis, showing gross bronchiectasis in both upper lobes.

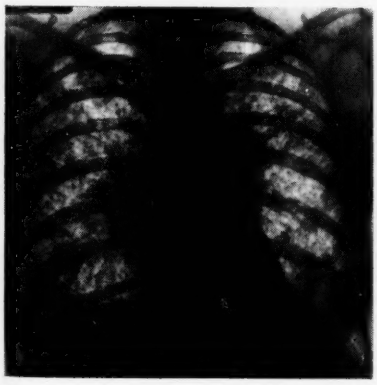

Fig. 8—Female, aged 47. Diffuse coarse nodular shadows due to pulmonary sarcoidosis, a year after bilateral hilar node enlargement discovered at an attack of iritis. A liver biopsy showed epithelioid cell follicles.

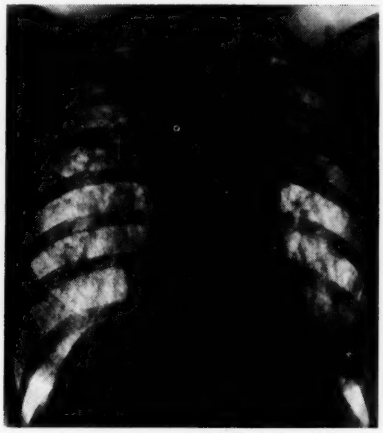

Fig. 9—Same patient as fig. 8. Radiograph taken 8 years later, showing severe fibrosis due to progressive pulmonary sarcoidosis (type III).

prognosis is also better in the absence of recognisable extrapulmonary sarcoidosis (table IV).

In this series 86% of patients without extrapulmonary sarcoidosis have improved, compared with 54% of those in whom it was found. For those who have extrapulmonary lesions the prognosis is again better where one site alone is involved (table V).

Fig. 11—Same patient as figs. 8, 9, and 10. Giant section of lung showing upper-lobe bronchiectasis and peribronchial fibrosis; also diffuse fibrosing sarcoidosis throughout the rest of the lung.

Here some 64% have improved, in contrast with only 44% where two or more extrapulmonary sites of sarcoidosis have been present. Sones and Israel (1960) have recently claimed that there is no difference in the prognosis between patients with less than three and those with three or more systems involved, if allowance is made for cutaneous sarcoidosis, which they regard as a deciding feature. Among the 17 of our 125 patients who had skin sarcoids other than erythema nodosum, there was no evidence of an unfavourable prognosis for their pulmonary lesions by comparison with the rest of the series or in relation to the number of other sites of extrapulmonary sarcoidosis. Age, sex, and tuberculin sensitivity also appear to be without prognostic significance. On the other hand uveoparotitis is apt to be associated with a prolonged active course. In 5 out of 13 patients who have had uveoparotitis the pulmonary disease has belonged to type III and has led to severe fibrosis. This compared with 20 in this category of the other 112 patients who have not had uveoparotitis.

Prognosis and Treatment

From our knowledge of its natural history and from these various pointers, it is usually possible to forecast the course which pulmonary sarcoidosis will take in the individual patient. Type I can often be recognised within a year and types II and III within two years, though the probable fate of pulmonary infiltration found initially or appearing after nodal enlargement may sometimes remain uncertain. Also it can be difficult sometimes to be sure, even as late as five years from discovery, whether persistent pulmonary infiltration will lead to progressive fibrosis in the long run.

It is clear, however, once the prognosis can be gauged, that patients with type-III disease which will lead to progressive lung destruction are in need of treatment. For those with type-II disease the need for treatment is limited because this type is compatible with good health and an active life. The fact that such patients have persistent radiographic changes is not by itself an indication for it. In this group the need for treatment is probably judged best by repeated assessment of lung fuction, particularly the diffusing capacity. Patients whose disease belongs to type I, with its self-limiting course, do not need treatment.

Although in this way our approach to the selection of patients for treatment becomes more logical, its use requires great caution if we are not to mistreat. Systemic corticosteroids are at present the only proven remedy for the suppression of the sarcoid follicle. There is ample evidence of this but there is no evidence that the fundamental mechanism responsible for sarcoidosis is affected; and if treatment is stopped before this mechanism has ceased to operate, then relapse is inevitable and swift (Hoyle, Dawson, and Mather 1955). This aspect of the action of corticosteroids is the key to their limitations as an effective form of treatment for pulmonary sarcoidosis. In disease of type III the active course extends for a decade or often longer; so that treatment with corticosteroids, if it is to be effective, is required for many years. In disease of type II the active course runs for at least several years—probably up to five years in many of these patients—so that treatment is again a long-term commitment if it is to be effective. All our experience, so far, confirms the need to regard in this way the duration of treatment which is required.

The problem of embarking on treatment with corticosteroids in the face of these requirements is fraught with uncertainties. It is probable, for patients whose disease belongs to type III, that the prognosis cannot be altered radically though disability may be limited and may be postponed while they are able to take corticosteroids. For most patients with disease of type II the outlook is so much better that the results of treatment far from justify its risks. On the other hand, those in this group who show increasing impairment of their diffusing capacity and exercise tolerance require treatment and might be expected to benefit if corticosteroids can control or abolish these defects during the few years of the active course of the disease. Here the aim of treatment is to convert the disease, if possible, from type II to type I, with a normal radiograph and lung function eventually. A pilot investigation on a few patients in my series has already shown the difficulty of achieving this result (Smellie, Apthorp, and Marshall 1961).

TABLE IV—RELATION BETWEEN PRESENCE OF CLINICAL EXTRAPULMONARY SARCOIDOSIS (E.P.S.) AND PROGNOSIS

—	Total	Number improved	% improved
Whole series ..	125	79	63
Without E.P.S. ..	35	30	86
With E.P.S. ..	90	49	54

TABLE V—RELATION BETWEEN EXTENT OF CLINICAL EXTRAPULMONARY SARCOIDOSIS (E.P.S.) AND PROGNOSIS

—	Total	Number improved	% improved
Total with E.P.S. ..	90	49	54
With one site of E.P.S.	47	30	64
With two or more sites	43	19	44

Conclusion

I have tried to show how the prognosis of pulmonary sarcoidosis may be guided by the recognition of three distinct types of the disease, and what this implies for treatment with corticosteroids. We need to discover why the disease runs a short self-limiting course in one group

of patients and is persistent and sometimes progressive in the others. We need to learn more about the ultimate fate of patients with disease of type II. Also, we need to learn more about the time in the natural history at which sarcoid lesions induce irreversible changes in the diffusing capacity of the lungs, and about the margin of time for which diffusion defects remain susceptible to the suppressive effects of corticosteroids upon the sarcoid follicle. It is in these directions that we look for future work to make prognosis more exact and the role of treatment more rational.

I wish to thank the many colleagues who referred their patients or who helped this work in other ways. Most of the credit belongs to successive members of our team (to Dr. J. Dawson, Dr. G. Mather, and Dr. R. Greenwood initially, and to Dr. V. Parsons and Dr. H. Smellie later); and also to Mr. M. P. Curwen for his generous help with the statistics. I am indebted to the editors of the *Quarterly Journal of Medicine* and to the Clarendon Press for permission to reproduce tables I, II, and III, and also figs. 10 and 11.

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THIOTEPA IN THE TREATMENT OF TUMOURS OF THE BLADDER

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THIS paper is a preliminary report on our experiences in treating vesical tumours with an alkylating agent, thiotepa (triethylene thiophosphoramide), instilled directly into the bladder.

One of the major problems of the urologist is the patient with multiple papillary tumours involving large areas of bladder mucosa. Papillary neoplasms are best treated by endoscopic techniques, and in our experience the majority are readily controlled in this way. But when the number of tumours is large, endoscopic control may be impossible, and an alternative method of treatment must be chosen. In the past we have used radioactive colloidal gold, and radioactive cobalt with bromine, to treat cases of this type. The results of both methods have been uniformly disappointing; and the incidence of irradiation cystitis and tumour recurrence high. More recently we have used supervoltage external irradiation, and have stopped giving radioactive isotopes, reserving total cystectomy for extensive recurrences which follow radiotherapy.

In recent years considerable interest has centred on the cancerocidal drugs, notably the alkylating agents, the antimetabolites, and the actinomycins; and, in the treatment of malignant effusions into the pleural and peritoneal cavities, these agents, directly instilled, have now replaced radioactive isotopes. This led us to consider administering these agents to treat multiple papillary tumours of the bladder and to palliate advanced infiltrating neoplasms.

The effects of these compounds on malignant neoplasms resemble the effects of ionising irradiation, and, in general, tumours which are most radiosensitive respond most to the cytotoxic action of the alkylating agents. Hence these drugs are often termed " radiomimetic ". Most bladder tumours are moderately radiosensitive; thus a high concentration of an alkylating agent introduced into the bladder could be expected to influence surface growths.

Thiotepa was selected for the initial clinical trials. Two factors had to be considered in choosing the specific regimen: the action of an alkylating agent on the normal bladder epithelium; and the possibility of absorption of the drug from the bladder.

Thiotepa is a relatively non-toxic substance, without the irritant properties of the nitrogen mustards; and injecting it into normal tissues and body cavities has few local adverse effects. Though it does produce necrosis of tissues composed of rapidly dividing cells (notably the bone-marrow, the cells lining the small intestine, and the germinal cells of the ovary and testis), cells with a low rate of mitotic division appear to be relatively immune. The normal bladder epithelium falls in the latter category and instilling thiotepa into the bladder seemed a safe procedure. Bateman (1955) reported introducing thiotepa into the bladder of a patient with an advanced neoplasm; a total dose of 250 mg. was given, and no adverse effect on the bladder observed. The total amount which could be safely introduced into the bladder is obviously limited by the proportion absorbed into the systemic circulation, with the risk of bone-marrow depression.

Methods

The Absorption of Chemical Substances from the Bladder

Maluf (1953, 1955) found that the bladder acts as a poorly permeable membrane in allowing the absorption of certain chemical substances by a process of simple diffusion. Thus urea, water, and sodium and chloride ions are all absorbed to some extent. Sodium iodide and sodium acetrizoate (' Urokon ') were both absorbed from concentrated solutions in amounts sufficient to produce pyelograms, but significant amounts of glucose and glycine were not.

Yeates (1960), who worked with various sulphonamides, noted the importance of molecular size in determining absorption from the bladder: sulphacetamide was absorbed and could be demonstrated in the blood, while sulphanilamide and sulphasolucin (' Soluseptazine ') could not. It appears that substances with a molecular weight over 200 are not absorbed to any extent; those of a smaller molecular weight are absorbed by simple diffusion, the rate depending on the concentration gradient between the plasma and the urine in the bladder.

The molecular weight of thiotepa is 189; it should therefore be absorbed. An attempt was made by a chemical method to estimate the amount absorbed. Glucose solution was instilled into the bladder, and over three hours no systemic absorption was detected; we recovered all the glucose introduced from the bladder contents. By a similar technique, 30 mg. of thiotepa in 100 ml. of sterile water was instilled into the bladder of 2 patients with multiple papillary tumours. After three hours the bladders were emptied and carefully washed out, the washings being added to the urine. In each case approximately 20 mg. of thiotepa was recovered from the bladder, representing a loss of one-third, presumably from absorption.

The Regimen

The dosage was therefore calculated on the assumption that one-third of the drug would be absorbed. We first gave small amounts of the drug, and then increased the amount gradually to a total of 300–400 mg. in divided amounts over eight to

fourteen days. Absorption of one-third of this would subject the patient to a systemic dose of 100–135 mg. Though individual variations are considerable, doses of this level in a patient of average weight without widespread bone metastases should not depress the marrow more than temporarily.

Doses of 30 mg. in 50 ml. sterile water were first given, and increased gradually to 90 mg. in 50 ml. Four doses were given in each case, every two to three days. The drug was retained for three hours. Recently 2 patients have been given four individual doses of 120 mg.

Technique of Administration

Moderate dehydration is produced by withholding fluids for twelve hours. A catheter is passed, the bladder emptied, and the drug introduced. The catheter is removed, and the patient instructed to void after three hours. Prophylactic sulphamethizole ('Urolucosil') is given to cover the period of treatment. A full blood-count is performed at the beginning of treatment and at weekly intervals for four weeks.

Method of Case Selection

16 patients have been selected for this form of treatment. The main indication is the presence of multiple papillary tumours with no clinical evidence of infiltration. 12 patients fell in this category. 1 patient with a solitary papillary tumour on the right wall of the bladder was included because a urethral stricture prevented the passage of a resectoscope and the tumour was too large for endoscopic diathermy. On histological examination, the tumour in each case has been a well-differentiated carcinoma with no evidence of invasion. 3 patients with a recurrent infiltrating neoplasm after megavoltage therapy were included in an attempt to reduce their hæmaturia. On histological examination, a poorly differentiated carcinoma of papillary and solid type was seen in each.

Results

Effects of Thiotepa on Bladder Function

3 patients complained of increased frequency and dysuria after treatment. In 1 case treatment was abandoned after two doses had been given. In all 3 a coliform organism was cultured from the urine; and the symptoms subsided rapidly after exhibition of an antibiotic. The part played by thiotepa in bringing about these symptoms is not clear; but it seems most likely that intermittent catheterisation caused the infections. No patient has complained of symptoms immediately after the drug has been instilled.

RESULTS OF TREATMENT

Case no.	Sex	Age (yr.)	Previous history	Condition of tumour before thiotepa: Site	Condition of tumour before thiotepa: Type	Date of treatment	No. and size of doses * (mg. in 50 ml. water)	Result	Other treatment	Final result
1	M	66	1958: transvesical resection of papillary tumour; multiple recurrences fulgurated transurethrally	Entire bladder-wall Lt. lateral wall	Multiple small papillary 2 larger tumours	Mar., 1960	4×30	$^{6}/_{52}$ and $^{12}/_{52}$: most smaller tumours gone; larger unchanged	July, 1960: transvesical diathermy excision of residual tumour	No recurrence since
2	M	62	1956: transurethral resection of papillary carcinoma of bladder neck. 1959: rt. nephroureterectomy for ureteric cancer	Bladder neck and posterior urethra Trigone	Multiple papillary carcinomas Single carcinoma	April, 1960	4×60	$^{6}/_{52}$ and $^{12}/_{52}$: no change	None	$^{6}/_{12}$: died. Chronic bronchitis and cardiac failure
3	M	69	1958: transurethral resection of papillary tumour. Recurrences fulgurated transurethrally	Anterior and lt. lateral wall; trigone	Multiple papillary well-differentiated transitional-cell carcinomas; no invasion	May, 1960	4×60	$^{6}/_{52}$: no change. $^{9}/_{12}$: small tumours gone, 3 larger tumours left	Transvesical diathermy excision	December, 1960: no recurrence
4	M	63	Pelvic fracture; urethral stricture. Resectoscope could not be passed. $^{6}/_{52}$: painless hæmaturia	Rt. lateral wall	1 papillary	June, 1960	4×60	$^{6}/_{52}$ and $^{12}/_{52}$: no change	October, 1960: tumour destroyed with Kidd's cystoscope	April, 1961: no recurrence
5	F	52	$^{8}/_{52}$: hæmaturia. Bimanual examination negative; intravenous pyelogram normal	Rt. lateral wall	Group of well-differentiated papillary carcinomas; no invasion	June, 1960	4×90	$^{6}/_{52}$: tumours white and necrotic $^{3}/_{12}$: bladder clear	$^{9}/_{12}$: small papillary tumour on trigone removed by diathermy	Aug., 1961: no recurrance
6	M	68	1940: transurethral fulguration of vesical papilloma; multiple recurrences similarly treated. 1953: radioactive cobalt for multiple tumours. May, 1960: hæmaturia. Bimanual examination negative	Anterior and rt. lateral walls	Multiple papillary well-differentiated carcinomas; no invasion	June, 1960	4×90	$^{6}/_{52}$: tumours necrotic $^{3}/_{12}$: bladder clear	None	$^{9}/_{12}$: bladder still clear
7	M	58	1957: two-year history of hæmaturia. Radioactive gold for multiple papillary tumours, diathermy for residue. Transurethral fulguration of recurrences. Bimanual examination negative	Rt. and lt. lateral walls; anterior wall	Multiple small well-differentiated carcinomas; no invasion	July, 1960 Mar., 1961	4×60 4×120	$^{6}/_{52}$: tumours on lateral walls gone, anterior wall tumours necrotic. $^{3}/_{12}$: necrotic tumour still present. $^{6}/_{12}$: many minute papillary tumours, rt. and lt. lateral walls and anterior wall $^{6}/_{52}$: small necrotic tumours, lt. lateral wall. Bladder otherwise clear	None	 July, 1961: no recurrence
8	M	53	1953: papillary tumour on lt. ureteric orifice removed by transurethral fulguration. Small recurrences similarly treated. 1957: radioactive gold to multiple posterior-wall tumours. Recurrences transurethrally fulgurated	All walls	Many small well-differentiated papillary carcinomas; no invasion	Oct., 1960 Jan., 1961	4×90 4† ×90	$^{3}/_{12}$: 1 residual tumour near lt. ureteric orifice, rest clear. $^{6}/_{12}$: 2 small tumours on lt. lateral wall, irregular mucosa on trigone $^{3}/_{12}$: 2 pinhead tumours on lt. lateral wall, rest clear	Tumour destroyed by diathermy Diathermy to tumours	 Aug., 1961: no recurrence

* Treatment on alternate days, except where otherwise stated.
† Treatment every 7 days.

Systemic Complications of Absorbed Drug

In 2 patients the blood-picture changed. In the first, who received two doses of 90 mg., the total leucocyte-count fell to 2000 on the fourteenth day after the last dose of thiotepa. The count returned to normal in seven days.

In the second multiple purpuric hæmorrhages developed on the sixteenth day after the last dose; the platelet-count at this stage had fallen to 100,000 and the leucocyte-count to 2000. The latter fell to a minimum of 350 on the twenty-first day. Cortisone and broad-spectrum antibiotics were given; and the blood-picture returned gradually to normal in seven days.

These cases have proved that substantial amounts of thiotepa are absorbed from the bladder. Our original estimate of one-third absorption in three hours is probably correct. We think that an individual dose of thiotepa of 90 mg., dissolved in 50 ml. sterile water, retained for three hours, and given on four occasions on alternate days, is probably the maximum safe dose; at this dosage the white-cell count may occasionally be depressed.

Effect on Tumour

Those cases which are going to respond start to do so in six weeks; and the maximum effect is apparent at twelve weeks. We deliberately selected patients with multiple small tumours, because these seemed most likely to respond. With bulkier tumours, we thought that the drug might not penetrate sufficiently. In practice this has proved to be the case: the bulkier tumours have remained unaffected; and the most satisfactory response was obtained when all the tumours were less than 0·5 cm. in diameter.

13 patients with papillary tumours have been treated. In 2 no effect was observed. The first had a bulky tumour and was included in our series because a urethral stricture made transurethral resection impossible; the second had multiple tumours involving the bladder base and posterior urethra.

3 patients responded incompletely; in 2 of these a large number of small papillary tumours disappeared, leaving a few bulkier neoplasms which were subsequently treated by transvesical removal. The third patient has been followed up for only six weeks, and only a partial response has been obtained so far.

In 8 patients multiple papillary neoplasms have almost completely disappeared; 2 of these patients have required two

RESULTS OF TREATMENT (*cont.*)

Case no.	Sex	Age (yr.)	Previous history	Condition of tumour before thiotepa		Date of treatment	No. and size of doses* (mg. in 50 ml. water)	Result	Other treatment	Final result
				Site	Type					
9	F	50	1954: cystodiathermy to multiple papillary tumours. 1955: radioactive gold and cystodiathermy to recurrences. Bimanual examination negative	Posterior and lateral walls	Multiple highly differentiated papillary carcinomas; no invasion	Jan., 1961	4×90	$^{6}/_{52}$: tiny necrotic tumour on lt. lateral wall. Rest clear $^{9}/_{12}$: Bladder clear	None	July, 1961: no recurrence
10	M	64	1946: transvesical excision of 2 large papillary tumours on lateral walls. Transurethral fulguration of recurrences. Bimanual examination negative	Anterior wall	Multiple well-differentiated papillary carcinomas	Mar., 1961	4×90	$^{6}/_{52}$: anterior-wall tumours gone. Tiny tumour near airbubble. Rest clear	Residual tumour destroyed by diathermy. Chloramphenicol for *Escherichia coli* infection	Aug., 1961: no recurrence
11	M	73	1960: $^{3}/_{12}$ intermittent hæmaturia. Bimanual examination negative	Rt. lateral wall Lt. lateral wall	1 papillary tumour 1 large, many small well-differentiated papillary carcinomas	Mar., 1961	2×90	Frequency and dysuria $^{6}/_{52}$: bladder free of tumour	Chloramphenicol for *E. coli* infection	June, 1961: no recurrence
12	M	58	1956: transurethral resection of large papillary tumour; transurethral fulguration of recurrences	Lateral and posterior walls	Multiple small well-differentiated papillary carcinomas; no invasion	Feb., 1961	4×120	$^{6}/_{52}$: single necrotic papillary tumour on rt. lateral wall. Rest of bladder clear	Tumour destroyed by diathermy	July, 1961: no recurrence
13	F	53	1940: suprapubic removal of papillary tumour. Cystoscopies and transurethral diathermy for recurrences. 1961: hæmaturia	Lt. lateral wall and anterior wall	Many papillary carcinomas; no invasion	Mar., 1961	4×120	Frequency after 2nd dose. $^{10}/_{365}$: purpuric hæmorrhages; pancytopenia $^{6}/_{52}$: lateral-wall tumours gone; tumour on anterior wall appears necrotic	Nitrofurantoin for *E. coli* infection. Cortisone and broad-spectrum antibiotic	July, 1961: tumour on anterior wall still present
14	M	67	1955: transurethral resection of 4 large well-differentiated papillary carcinomas. Transurethral fulguration of recurrences. 1959: megavoltage therapy to recurence at neck, poorly differentiated carcinoma. Persistent hæmaturia. Cystectomy refused. Bimanual examination: palpable tumour invading muscle	Rt. lateral wall Above rt. ureteric orifice	Recurrence of poorly differentiated carcinoma Mucosal papillary tumours	Nov., 1960	4×60	$^{3}/_{12}$: lateral-wall tumour unaltered. Papillary tumours gone	None	Hæmaturia less frequent
15	M	75	1956: transurethral resection of extensive well-differentiated carcinoma infiltrating muscle. Radical megavoltage therapy. $^{6}/_{12}$: cystodiathermy of recurrences with Kidd's cystoscope. Tumour palpable; persistent hæmaturia. General condition poor; unfit for cystectomy	Anterior wall and trigone	Multiple papillary recurrences	Nov., 1960	4×60	$^{1}/_{52}$: hæmaturia stopped	Unfit for anæsthesia; cystoscopy not attempted	Died: carcinoma of bladder
16	M	75	1959: hæmaturia $^{3}/_{12}$. Large, well-differentiated transitional-cell carcinoma, palpable by bimanual examination. General condition poor. Palliative X-ray therapy. October, 1960: hæmaturia recurred	Rt. lateral wall	Necrotic tumour	Nov., 1960	4×60	Hæmaturia persisted	Palliative X-ray therapy	Died: carcinoma of bladder

*Treatment on alternate days.

separate courses of treatment to achieve this, while 4 needed diathermy destruction of minute residual tumours which might have responded to a further dose of thiotepa.

Effect on Hæmaturia

In 3 patients with infiltrating neoplasms and persistent hæmaturia, the hæmaturia ceased in 1, in 1 it decreased considerably after treatment, but in the 3rd there was no response.

Discussion

Our series was small and the follow-up very short; but it seems clear that thiotepa introduced into the bladder may totally or partially destroy certain kinds of papillary tumour, but has little or no adverse effect on the normal bladder epithelium.

A large molecule is necessary if the drug is not to be absorbed; but papillary bladder tumours are not unlike normal bladder epithelium in basic structure, and diffusibility may be essential for an anti-tumour drug to be effective.

The concentration of the drug and the length of time the tumour is exposed to its action are important. We think that the highest concentration of the drug the bladder will tolerate should be administered, because the drug is progressively diluted by urine. The concentration of the drug could be increased and the treatment time lengthened by temporarily diverting the urine with ureteric catheters. Less of the drug could then be given, and the general effect of absorption minimised; but what is now a relatively simple technique would become complicated and would carry the slight hazard of implanting tumour and spreading infection higher in the urinary tract. Since we have obtained a therapeutic effect without this additional step, and absorption of the drug has not proved a serious risk, we have not adopted this procedure.

Further clinical trials with different anti-tumour drugs are required. A method of estimating the sensitivity of a specific tumour to a specific agent would be very valuable. Tissue-culture may provide this information. We hope the procedure can be further developed for treating papillary tumours of the bladder, either alone or as an adjunct to other endoscopic techniques.

Summary

Vesical tumours were treated by injecting thiotepa, an alkylating agent, directly into the bladder.

Of 13 patients with papillary tumours treated, these almost completely disappeared in 8.

Thiotepa seems to act best on small tumours.

We would like to express our indebtedness to Mr. C. J. L. Thurgar for his encouragement, and to the British Empire Cancer Campaign for financial help.

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". . . The sole use of instruments is to obtain information; they have no relevance to the purpose for which the data are sought or the use that is made of them when obtained. It is a salutary thought worth keeping in mind, therefore, that we are no better off, for all our instruments, than our predecessors through the ages in the essential endeavour of research—understanding . . . once the intellectual requirement of clear purpose is relaxed, it is a short step to the gathering of data becoming an end in itself, to the instruments dictating the research rather than the research using the instruments. The philosophy of Wilkins Micawber has never led to any worthwhile results either in life or research."—Sir HAROLD HIMSWORTH *in Tools of Biological Research*, third series; p. IX. Oxford: Blackwell. 1961.

PRIMARY ALDOSTERONISM

The Value of Spironolactone in Diagnosis

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IN most of the thirty reported cases of primary aldosteronism hypertension has been associated with hypokalæmic alkalosis. Conn (1955) suggested, in describing the syndrome, that three previously reported examples of potassium depletion associated with renal disease also had primary aldosteronism (Earle et al. 1951, Evans and Milne 1954, Wyngaarden et al. 1954); and further investigation of one of these confirmed the presence of an aldosterone-producing adrenal tumour (Milne et al. 1957).

The case we now discuss was previously reported as having chronic hypokalæmia of renal origin (Sayers et al. 1955); but we have since shown that this diagnosis was incorrect, and an adrenal adenoma has been removed.

With the development of the 17-spirolactones, which are aldosterone antagonists, a new method has become available for investigating possible cases of primary aldosteronism. Conn et al. (1958) and Salassa et al. (1958) reported the effects of an early spirolactone, SC–8109, in patients with this condition. More recently Bartter (1960) and Simpson and Barnett (1960) have used the more potent spironolactone (SC–9420), and this has proved valuable in the diagnosis of our case.

Case-report

This patient's clinical history has previously been reported in detail (Sayers et al. 1955):

She first had transient episodes of weakness and paralysis after the delivery of her third child in 1952, when she was 36. The weakness lasted several days, sometimes preventing her from walking or supporting herself. During each pregnancy a high blood-pressure (160/100 mm. Hg) had been observed. This was known to have reverted to normal after the second delivery, but in 1952 it was 165/100. Also in 1952, nocturia, polyuria, and frequency of micturition developed, associated with a bizarre visual disturbance in which only central vision remained intact. There was evidence of generalised muscle weakness, with a serum-potassium level of 2·4 mEq. per litre. Other abnormal findings, apart from an electrocardiogram consistent with hypokalæmia, were a urea-clearance test of 50%, and an impaired specific-gravity-concentration (S.G.C.) test of 1016 after 19 hours' fluid deprivation. The glucose-tolerance test was "flattened", and an intravenous pyelogram showed minor distortion of the upper calyces on the right.

The patient was given replacement therapy with potassium chloride 24 g. daily (322 mEq. of potassium). A month after this was started the S.G.C. test had improved to 1022, and during the next year on this large dose her serum-potassium remained within normal limits.

In 1953 the endogenous creatinine-clearance test was normal (124 ml. a minute), although the effective renal plasma-flow was reduced to 432 ml. a minute, as measured by *p*-aminohippuric-acid clearance. The daily aldosterone excretion was within normal limits when measured by Dr. Joseph Bornstein in Melbourne, and this was regarded as strong though not absolute evidence against primary aldosteronism.

From 1953 until 1960 regular potassium supplements were given of 8–12 g. potassium chloride a day. The serum-

potassium during this time remained within normal limits, and the patient felt well and was free of symptoms.

Recent Investigations

Early in 1960, after 8 years on potassium supplements, the added potassium was stopped for a trial period, and the serum-potassium fell from 4 to 2·7 mEq. per litre in 21 days. The blood-pressure on admission to hospital for reassessment was 160/110, and clinically there was evidence of moderate left ventricular hypertrophy, but no other abnormalities were found. The serum-sodium was 145, the serum-potassium 3·25, the plasma-chloride 99, and the plasma-carbon-dioxide content 26·8 mEq. per litre, and the blood-urea was 33 mg. per 100 ml.

Urine examination showed no evidence of chronic infection, and repeated cultures were sterile. Renal function was almost normal, the S.G.C. test was 1022 after 18 hours' fluid deprivation, the glomerular filtration-rate as measured by inulin-clearance was 145 ml. per minute, and the renal plasma-flow measured by *p*-aminohippuric-acid clearance was 516 ml. per minute. Acidification of the urine after an acid-load test (Wrong and Davies 1959) showed impaired ability to excrete acid urine; the urinary pH, which was 6·9 before the acid load, fell only to 6·1 after giving ammonium chloride (0·1 g. per kg. body-weight).

The glucose-tolerance test remained impaired, with a 2-hour blood-glucose of 205 mg. after 100 g. of glucose. An intravenous pyelogram with tomography showed the right kidney to be 13·6 cm. long, and the left 13·8 cm.; the renal pelves were small, the calyces tended to be long and slender, and there was an unusual appearance in the right upper calyces suggestive of chronic pyelonephritis. Retroperitoneal insufflation of air showed appearances suggestive of enlargement of the left adrenal gland.

Because of the equivocal findings, a balance study with spironolactone was made as indicated in the figure (*a*). Throughout, the patient was given a diet containing sodium 90 mEq. and potassium 76 mEq.; in addition potassium 40 mEq. was given as potassium-chloride supplements. After 5 days, spironolactone 1200 mg. was given daily for 4 days. During this period the daily urinary sodium output increased from a mean of 72 mEq. to a maximum of 136 mEq., and the daily urinary potassium output fell steadily from a mean of 74 mEq. to 26 mEq. on the 4th day of therapy. The urinary sodium/potassium ratio, which had been about 1/1, rose to 4/1 by the 4th day and returned to below 1/1 after the spironolactone was stopped. The change in salivary sodium/potassium ratio was less convincing: it rose from 0·29 to 0·51, to fall again to 0·34. These findings implied that aldosterone was being produced by the adrenal gland in excessive amounts during the period of normal sodium intake.

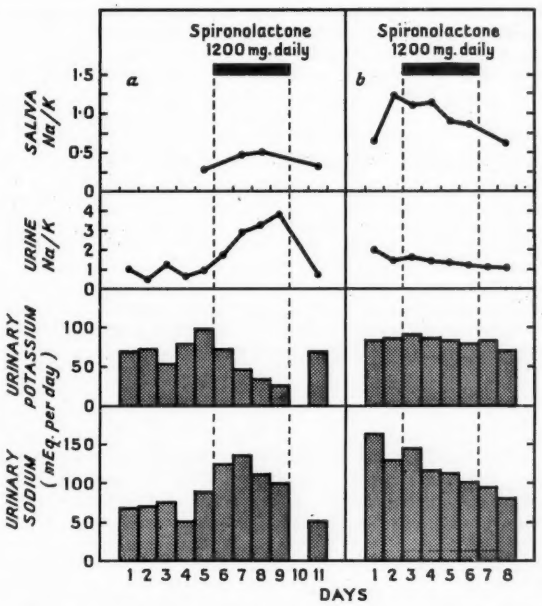
The patient was therefore given a supplement of potassium 200 mEq. a day for 10 days before operation. After replacement of the cumulative potassium deficit of 770 mEq. a further renal acid-load test still showed impaired ability of the kidneys to acidify the urine when the urinary pH was falling from 6·8 to 6·1, after an acid load of ammonium chloride.

Operation and Progress

At operation a small adrenal adenoma, 2 cm. in diameter, was removed from the left adrenal gland by Mr. F. P. Furkert.

Afterwards the patient required no further potassium supplements, and she made an uneventful recovery. Although the potassium was stopped on the day of operation, she remained in positive potassium balance (64 mEq.) during the first week after operation, and the blood-pressure fell to 120/75.

The case was reassessed 3 months after operation. During this interval the patient had taken a normal diet without potassium supplements. The serum-potassium was 4·7 and the serum-sodium 145 mEq. per litre, and a renal acid-load test showed that the ability of the kidneys to excrete acid urine had been restored, the pH falling from 6·6 to 4·9. The blood-pressure was 120/80. When the patient was given the same diet and potassium supplement as during the first balance period before operation, the same dose of spironolactone (see figure [*b*]) did not influence the sodium or potassium excretion of the kidney, and did not alter the urinary sodium/potassium excretion ratio.



Effect of spironolactone (1200 mg. per day) on the daily urinary sodium and potassium content in a patient with primary aldosteronism (*a*) before operation, and (*b*) after removal of an adrenal adenoma.

The daily sodium and potassium intakes were 90 and 116 mEq. respectively.

Discussion

Primary aldosteronism can be caused by an adenoma, a carcinoma, or bilateral hyperplasia of the adrenal glands. It is often impossible to demonstrate an adrenal tumour by retroperitoneal oxygen insufflation, and other tests are necessary to diagnose primary aldosteronism before operation. The most direct method is to measure the secretion-rate of tritium-labelled aldosterone, but this technique is available only in a few research laboratories. It is less reliable to measure the daily urinary output of aldosterone, and the results do not always correlate well with the secretion-rate of aldosterone by the adrenals (Nabarro 1960).

Aldosterone antagonists provide a means—within the scope of any hospital laboratory—of studying indirectly the effects of aldosterone. Spirolactones have been used in primary aldosteronism in thirteen previously reported cases (see table). The early spirolactone was used in eight cases, and spironolactone was given in the other five, and in the one here reported. Treatment lasted from 2 to 8 days, and the dose used varied widely. This variation is important because spirolactones cause partial blocking of aldosterone below the maximum dose required for a full effect (Biglieri 1960). The diet during the test is also important because in a normal patient a low-sodium diet will cause a significant rise in the secretion of aldosterone (Conn et al. 1958, Luetscher and Lieberman 1958). With spironolactone the optimum dose is 1·2–1·6 g. per day.

The aldosterone antagonists, by blocking the action of aldosterone, caused a definite change in both urinary sodium and potassium excretion in eleven of the fourteen

SPIRONOLACTONE IN THE DIAGNOSIS OF PRIMARY ALDOSTERONISM

Author	Patient's Sex	Patient's Age (yr.)	Sodium in diet	Spironolactone Type	Spironolactone Dose (g.)	Spironolactone Duration (days)	Urinary sodium with spironolactone* (mEq. per day) Before (aver.)	Urinary sodium with spironolactone* (mEq. per day) During (max.)	Urinary potassium with spironolactone* (mEq. per day) Before (aver.)	Urinary potassium with spironolactone* (mEq. per day) During (min.)	Urinary aldosterone* (µg. per 24 hr.) Before	Urinary aldosterone* (µg. per 24 hr.) During	Comments
Conn et al. (1958)			Very low	SC-8109	?	?	?	?	?	?	?	?	Definite antagonism
Salassa et al. (1958)	F	49	High normal	,,	1	4	120	240	55	30	32, 56	105, 73	,,
Wrong and Gowenlock (1958)	F	35	,,	,,	0·5	3	?	?	?	?	25–33	Unchanged	,,
Kistler et al. (1959)	F	52	?	,,	1·2	4	?	?	?	?	?	?	,,
Bartter (1960)	F	35	Low normal	,,	1·0 0·7	1 5	10	80	65	30	195–220	220, 195, 190	,,
	M	46	Normal	,,	1·0 0·7	1 3	80	100	80	30	32, 30	20, 50, 40, 37	Effective only on potassium
	M	7	Low normal	,,	0·7 1·0	3 1	50	72	170	150	40, 40	60–120	No antagonism
Genest (1960)	F	15	Normal	,,	1·2	2	120	180	115	80	?	?	Definite antagonism
Biglieri (1960)	M	25	Normal	SC-9420	0·8 1·2	1 1	100	160	130	30	50	95	Definite antagonism
	F	39	,,	,,	0·8 1·2	3 2	100	155	80	30	24	30, 55	,,
Laragh (1960)	F	17	Very low	,,	0·4	6	20	60	50	60	?	?	Effective only on sodium
Peterson (1960)	F	49	High normal	,,	0·4 0·8	5 3	120	195	110	80	56–83	120–140	Definite antagonism
Simpson and Barnett (1960)	F	37	Normal	,,	1·0 2·4	3 1	130	200	70	45	?	?	,,
Present case	F	45	,,	,,	1·2	4	72	136	74	26	?	?	,,

*Some figures have been estimated from graphs.

cases. In one of the others there was sodium diuresis alone, in another potassium excretion fell but the urinary output of sodium was unchanged, and in the third (Bartter 1960) the urinary sodium and potassium excretion were not significantly changed.

The true value of spironolactone in the diagnosis of primary aldosteronism remains uncertain. In our patient, the spironolactone test, repeated under similar circumstances after the aldosterone-producing tumour had been removed, did not show a significant change. Between the first and the second balance studies a cumulative potassium deficit of 770 mEq. was replaced, and this in itself might have influenced the aldosterone secretion. But it is more probable that the tumour, which caused the depletion of potassium, was secreting aldosterone independently of the total body-potassium. The only other report of the administration of a spirolactone postoperatively is that of Salassa et al. (1958), in which SC-8109 1·9 g. was given on the 3rd and 4th days, when there was a sodium diuresis and no measurable aldosterone in the urine. The aldosterone antagonist did not influence the urinary sodium/potassium ratio.

Impaired renal function, which occurs in many cases of primary aldosteronism, has been attributed to potassium depletion (Milne et al. 1957). In our case the capacity of the kidneys to concentrate urine was restored when the potassium deficit was corrected before the adenoma was removed. The impaired capacity of the kidneys to excrete acid, however, persisted after the potassium deficit was replaced. When the acid-load test was repeated 3 months after operation, the pH of the urine was 4·9, which is within the normal range (Wrong and Davies 1959). This would support Wrong and Gowenlock's contention (1959) that the defect of acidification is a direct result of excess aldosterone secretion and is not secondary to potassium depletion, as proposed by Milne et al. (1957). The mechanism of the defect in acidification in the renal tubule remains uncertain. Aldosterone acts at a level in the tubule where the sodium ion is exchanged either for potassium or hydrogen ion; and Stanbury (1958) suggested that, by facilitating the tubular secretion of potassium ion, aldosterone may inhibit the secretion of hydrogen ion and so prevent acidification of urine. But this does not explain the increased excretion of ammonia observed in some patients (Wrong and Davies 1959).

Our patient kept very well during the 7 years on potassium supplements, and the long delay before removal of the adenoma does not seem to have affected the prognosis.

Summary

In a case of primary aldosteronism due to an adenoma of the adrenal gland, spironolactone, an aldosterone antagonist, was helpful in diagnosis before operation. The case has previously been reported incorrectly as one of chronic hypokalæmia of renal origin.

We wish to thank Mr. F. P. Furkert, senior surgeon to the Auckland Hospital, who removed the adrenal adenoma; and Mr. J. Pybus, who is supported by the Auckland Medical Research Foundation, for biochemical assistance.

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HEPATITIS CAUSED BY THE NEWER AMINE-OXIDASE-INHIBITING DRUGS

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DRUGS which inhibit monoamine oxidase (M.A.O.) now have a recognised place in the treatment of mental depression, and they have more recently been used for cardiac ischæmic pain (Towers and Wood 1958) and in rheumatoid arthritis (Scherbel and Harrison 1959). The original and most widely used of these agents, iproniazid, may cause liver damage, which (although uncommon) carries a high mortality (Popper 1958). This has led to the introduction of other M.A.O.-inhibiting drugs which are reputed to be less likely to damage the liver. Like iproniazid, five of the six such drugs currently available in this country are hydrazine derivatives (see table). Only one of the six, pheniprazine, has been reported to cause jaundice; Beer and Schaffner (1959) described a case of fatal hepatic necrosis, and Phear and Walker (1960) mentioned hepatic damage in 1 of 12 patients treated with it.

M.A.O.-INHIBITING DRUGS IN CURRENT CLINICAL USE

Substance	Official name	Proprietary name
*N-iso*Nicotinoyl-*N- iso*propylhydrazine	Iproniazid	'Marsilid'
α-methylphenethylhydrazine ..	Pheniprazine	'Cavodil'
		'Catron'
N-(2-Benzylcarbamlethyl)-*N* - *iso*nicotinylhydrazine	Nialamide	'Niamid'
Phenethylhydrazine	Phenelzine	'Nardil'
1-Benzyl-2-pivaloylhydrazine ..	..	'Tersavid'
3-*N*-Benzylhydrazinocarbonyl-5-methyl*iso*xazole	Isocarboxazid	'Marplan'
trans (±)-2-Phenyl*cyclo*propylamine	Tranylcypromine	'Parnate'
		'Parstellazine'

We now report jaundice which followed the administration of M.A.O.-inhibitors on six occasions in 4 patients. In three instances this was associated with pheniprazine therapy, and in three with nialamide, phenelzine, and iproniazid respectively.

Case-reports

THE FIRST PATIENT

A housewife began to have angina pectoris at the age of 44, followed three years later by cardiac infarction. During the next five years her chest pain became a severe disability, necessitating many admissions to hospital, and continuous anticoagulant therapy with phenindione ('Dindevan'). At 52, treatment with iproniazid was given, but this had to be discontinued four weeks later because of malaise, dizziness, and vomiting, followed within a day or two by jaundice. These symptoms subsided within two weeks of stopping the drug. During the next two years her activities were drastically restricted by anginal pain which was only partially relieved by cervical sympathectomy.

After a further admission to hospital in status anginosus, anticoagulant therapy was supplemented by pheniprazine 6 mg. b.d. This caused an improvement in her symptoms, but after seven months she suddenly had anorexia and malaise, followed three days later by jaundice and continuous upper abdominal pain. When admitted to hospital two weeks later she looked ill and was moderately jaundiced, with intense palmar erythema. The liver edge was 3 fingerbreadths below the right costal margin, and extremely tender. The serum-total-bilirubin was 12 mg. per 100 ml., zinc-sulphate turbidity 18 units, thymol turbidity 8 units, and alkaline-phosphatase 36 units.

On the assumption that this was a toxic hepatitis, both phenindione and pheniprazine were discontinued. For two weeks she remained critically ill, but then the jaundice and hepatic tenderness began to subside. By this time cardiac pain was almost continuous, and phenindione was cautiously restarted without recrudescence of jaundice. Within six weeks the jaundice had completely subsided, and the liver-function tests had returned to normal.

The patient died two months later, at the age of 54, after a further cardiac infarction. Necropsy was not obtained.

The first attack of jaundice appeared to be caused by iproniazid, and the second by pheniprazine, of which she had about 2500 mg. over seven months. Although jaundice has been reported with phenindione therapy, this drug seemed blameless here, since it was restarted before the jaundice had subsided without affecting recovery.

THE SECOND PATIENT

A housewife of 60 was admitted to a psychiatric unit in December, 1959, because of anxiety and loss of confidence which had not responded to outpatient treatment with imipramine. Pheniprazine 6 mg. b.d. brought about a steady improvement, and she was discharged three months later. This drug was discontinued six days after discharge, in March, 1960, when she was admitted to another hospital having vomited about a pint of bloodstained fluid. She was not anæmic (the hæmoglobin never fell below 100% (14·8 g. per 100 ml.), and barium-meal examination showed no abnormality.

Pheniprazine was restarted in May, because the psychiatric symptoms had recurred, and it was continued in a dosage of 6 mg. b.d. A month later it was stopped because of malaise, anorexia, and jaundice. In July when jaundice had been present for six weeks, she was admitted to a medical ward. She was

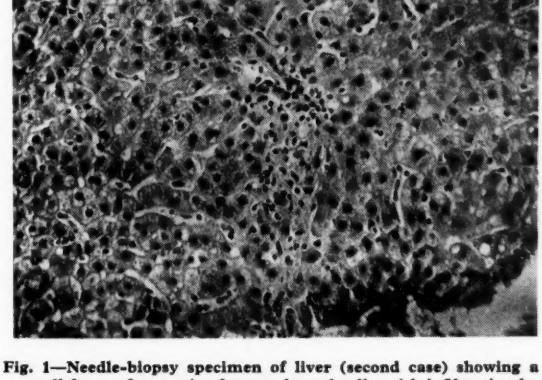

Fig. 1—Needle-biopsy specimen of liver (second case) showing a small focus of necrosis of parenchymal cells, with infiltration by inflammatory cells and well-marked fatty change (×165).

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slightly icteric, and the liver edge was 2 fingerbreadths below the costal margin. The serum-bilirubin was 3·3 mg. per 100 ml., zinc-sulphate turbidity 12 units, and thymol turbidity 6·5 units. A needle-biopsy specimen of the liver (fig. 1) showed patchy necrosis of liver cells and infiltration of the portal tracts by neutrophils, lymphocytes, and fibroblasts. There was much variation in nuclear size of the parenchymal cells, and many contained fat-droplets. Œsophagoscopy revealed a single varix on the anterior wall, but intrasplenic pressure (13 cm. of water) was within normal limits. The jaundice subsided with three weeks of admission, and the liver diminished in size.

In October, six weeks after discharge from hospital, her recovery from hepatitis seemed almost complete but her anxiety and loss of confidence had returned. Another M.A.O.-inhibitor, nialamide, was prescribed, in a dosage of 25 mg. t.d.s., by her doctor. When seen in the clinic after three weeks on this drug, she complained of nausea and anorexia, and she was found to be jaundiced again. The liver was 3 fingerbreadths below the costal margin. The serum-bilirubin had risen to 3·0 mg. per 100 ml., and the zinc-sulphate turbidity to 20 units. The jaundice subsided after three weeks, the liver again diminished in size, and the liver-function tests returned to normal. Four months after this second episode she was well, and the thirty-minute bromsulphalein retention was only 6%.

The previous history of hæmatemesis, and the finding of an œsophageal varix raised the possibility that the M.A.O.-inhibiting drugs caused an exacerbation of a pre-existing liver lesion. But after each episode of jaundice the liver returned to normal size, and biopsy showed nothing to suggest portal cirrhosis. The total dose of pheniprazine before the first attack of jaundice was about 1500 mg., and that of nialamide before the second attack was 1600 mg. It seems probable that these drugs were the cause of the hepatitis.

THE THIRD PATIENT

A student, aged 27, was treated for depression with chlorpromazine in September, 1960. Although this produced an immediate improvement he later relapsed, and treatment with pheniprazine was started in December, in a dosage of 12 mg. daily. This was reduced to 6 mg. daily, but later increased again to 18 mg. daily. On Feb. 22, 1961, after sixty days' treatment, upper abdominal discomfort, anorexia, and jaundice developed. The drug was immediately discontinued, but the jaundice progressively deepened, and on Feb. 27 the total serum-bilirubin was 22 mg. per 100 ml. The anorexia persisted, and by March 12 he had become intensely jaundiced with serum-bilirubin of 40 mg. per 100 ml, alkaline-phosphatase 26 units, zinc-sulphate turbidity 4 units, and thymol turbidity 3 units. His condition remained critical, and by March 23 he had become drowsy and somewhat confused. A needle-biopsy specimen of the liver showed necrosis of liver cells, with loss of lobular structure and invasion by inflammatory cells. Treatment with prednisone was started, but he collapsed and died later that day.

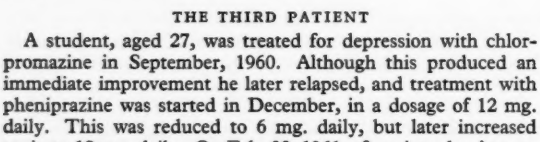

Fig. 2—Section of liver (third case) showing extensive necrosis of parenchymal cells and moderate inflammatory-cell infiltration (×165).

At *necropsy* the body was deeply jaundiced. The peritoneal cavity contained 3 pints of blood. The liver weighed 1370 g., and was brownish in colour with yellow mottling. A small puncture wound marked the site of the biopsy. The spleen was normal in size, and the kidneys showed early necrosis of the convoluted tubules with extravasation of blood into the tissue adjacent to the pelvis. No relevant abnormality was found in other organs. Microscopy of the liver revealed almost complete necrosis of the hepatic cells except for a zone immediately beneath the capsule. Infiltration by polymorphonuclear leucocytes and lymphocytes was present (fig. 2).

It seems probable that pheniprazine was the cause of the jaundice; the total dose was 560 mg. given over sixty days. Although all drugs were stopped when the jaundice started, the liver lesions progressed to almost complete necrosis over the next month.

THE FOURTH PATIENT

A housewife, aged 56, with depression, had for five months been taking phenelzine (originally 90 mg. daily, later 30 mg. daily) when she suddenly got pruritus, pain behind the eyes, and anorexia, and noticed that she was becoming yellow. Phenelzine was stopped after a total dose of 6300 mg. When she was admitted to a medical ward three weeks later her jaundice was slight, and a non-tender liver edge was only just palpable. The serum-bilirubin was 2·8 mg. per 100 ml., zinc-sulphate turbidity 13·5 units, alkaline-phosphatase 31 units, and serum-glutamic-pyruvic-transaminase 130 units. A needle-biopsy specimen of the liver (fig. 3) showed a patchy necrosis of parenchymal cells, with variation in nuclear size of the intact cells. The portal tracts and the necrotic areas were infiltrated by lymphocytes. Two weeks later the jaundice had subsided, and the serum-bilirubin had fallen to 0·2 mg. per 100 ml. She made an uneventful recovery.

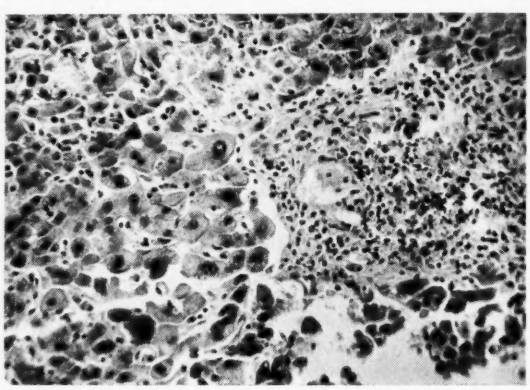

Fig. 3—Needle-biopsy specimen of liver (fourth case) showing patchy necrosis, heavy inflammatory-cell infiltration, and variation in nuclear size in the parenchymal cells (×165)

Discussion

Many of the newer M.A.O.-inhibiting drugs appear to carry an appreciable risk of liver damage of the type caused by iproniazid. Comparison of the incidence of jaundice induced by iproniazid with that induced by the newer M.A.O.-inhibitors is not possible, because experience with these is as yet not extensive. Moreover the frequency of jaundice in patients treated with iproniazid is uncertain. Rosenblum et al. (1960) analysed twelve reported series totalling 834 patients and found 11 cases of jaundice—an incidence of 1·4%. In contrast Scherbel and Harrison

(1959) did not encounter jaundice in 921 patients treated with this drug.

Although estimates of the frequency with which liver damage complicates iproniazid therapy vary, it is generally accepted that it carries a high mortality, which has been estimated at 15% (*New England Journal of Medicine* 1958). It seems that the mortality from hepatic damage caused by the newer M.A.O.-inhibitors is correspondingly high; with pheniprazine, 2 of the 5 cases recorded to date have been fatal.

Clinically liver damage caused by M.A.O.-inhibitors resembles viral hepatitis in that it is accompanied by anorexia and constitutional upset. But in our experience the illness has been more severe than viral hepatitis, and the jaundice caused by M.A.O.-inhibiting drugs has persisted or progressed for many weeks after the drugs have been discontinued.

Serial liver-function tests—notably the glutamic-pyruvic and glutamic-oxaloacetic transaminases—have been recommended to reveal the likelihood of jaundice (Pare and Sandler 1959). But, while the transaminase levels are almost always raised when jaundice has developed, their value in its prediction is less certain (Katz et al. 1959).

The liver damage produced by the newer M.A.O.-inhibiting drugs is similar to that caused by iproniazid. It is characterised by necrosis of liver cells, which may be patchy as in the second and fourth patients, or almost universal as in the third patient, and is accompanied by cellular infiltration in the portal tracts. If jaundice has previously been induced by one of the drugs of this series, the risk of recurrence when another M.A.O.-inhibitor is given seems great; 2 of our patients became jaundiced again when a second drug was given. Thus all M.A.O.-inhibiting drugs are best avoided once jaundice has occurred.

Each of the drugs which has caused jaundice is a derivative of hydrazine, itself a potent hepatotoxic agent in laboratory animals (Yard and McKennis 1955). Liver damage has not as yet been reported with tranylcypromine, which is the only non-hydrazine derivative of the series.

The liver lesions caused by M.A.O.-inhibitors are probably due to idiosyncrasy, because the hepatic damage cannot be equated with total dosage of the drugs. When given to animals, iproniazid rather surprisingly causes nothing more than slight fatty infiltration of the liver cells, and the necrotic lesions seen in M.A.O.-inhibitor hepatitis in man are not encountered (Zbinden and Studer 1959). Pretreatment with iproniazid in the rat enhances the liver necrosis induced by carbon tetrachloride; and, because the histology of human M.A.O.-inhibitor hepatitis resembles that of viral hepatitis, the tenuous hypothesis that M.A.O.-inhibitors cause jaundice by activating a latent viral hepatitis has been advanced by Popper (1958).

Pyridoxine deficiency induced by these drugs is an alternative mechanism invoked to explain the liver damage, and Coursin (1959) found low levels of circulating pyridoxal and pyridoxamine in a patient showing iproniazid toxicity. But the concomitant administration of pyridoxine does not prevent hepatic damage during treatment with M.A.O. inhibitors. One of our patients with severe hepatic damage, after treatment with iproniazid, had taken pyridoxine throughout.

She was a domestic cleaner, aged 41, who was admitted to a psychiatric unit in October, 1959, with a five-year history of anxiety and depression. After thiopentone narcosis, iproniazid was started in a dosage of 50 mg. b.d., together with pyridoxine also in a dosage of 50 mg. b.d. After five months' treatment, and a total of 15 g. of iproniazid, she became extremely tired and lost her appetite. A week later jaundice developed but she continued on the drug until she was admitted to hospital three weeks later by which time she had persistent vomiting and pruritus.

She was then a well-nourished, moderately jaundiced woman showing no spider nævi or palmar erythema. The liver and spleen were not palpable and there was no ascites or œdema. The serum-bilirubin was 8·2 mg. per 100 ml., zinc-sulphate turbidity 19 units, and thymol turbidity 10 units. Iproniazid was discontinued, but she remained severely ill and became increasingly icteric and developed fœtor hepaticus. Three weeks after admission to hospital, treatment with prednisone was started, and she made a steady recovery.

Summary

Hepatitis, which was fatal in a young man, has appeared after treatment with three of the newer monoamine-oxidase inhibitors. This was associated with pheniprazine in 3 patients, one of whom had a recurrence when nialamid was given at a later date, and with phenelzine in a fourth patient.

In 2 patients jaundice recurred when another drug of this series was given. Thus treatment with these drugs is inadvisable once liver damage has been sustained.

The dominant histological feature was liver-cell necrosis, which varied from being patchy to being almost total, and which was associated with infiltration by inflammatory cells.

We are indebted to Dr. D. J. Gee, and H.M. Coroner for the Craven district of the West Riding of Yorkshire, for the postmortem report on the third case.

We should also like to thank Dr. J. S. Hughes, Dr. J. C. Little, Dr. S. M. MacEntee, Dr. R. N. Tattersall, Dr. John Valentine, and Dr. William Whitaker who referred these patients to us.

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TRIPLE MOSAICISM OF THE SEX CHROMOSOMES IN TURNER'S SYNDROME AND HIRSCHSPRUNG'S DISEASE

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SEVERAL examples of mosaicism of the sex chromosomes in man have been described during the past three years (table I), and in all of them the pattern of mosaicism was of two cell types only. In both cases reported here three cell types are involved, and the possibility of mosaicism was suggested by a distinctive sex-chromatin pattern in the buccal smear.

Case-reports

THE FIRST CASE

This girl is the second child of a family of three. Her two brothers and both parents show no developmental abnormalities. The father is 6 ft. tall, and the mother 5 ft.; she had open

pulmonary tuberculosis during pregnancy. The patient weighed 6 lb. at birth, and she progressed well until she had tuberculous meningitis at 11 months. She remained under medical care until she could attend a residential school for the educationally subnormal. At 7 years her I.Q. was 64.

The girl was referred to Prof. D. V. Hubble at the age of 10, because of dwarfism and mental retardation. She was short and slim, with small bird-like facial features (fig. 1). Her height was 3 ft. 8 in. (50th percentile, 4 ft. 6 in.), weight 3 st. (50th percentile, 4 st. 10 lb.), arm span 42 in., and chest circumference 24 in. Her head circumference (19 in.) was slightly below average, and the hair line was normal. There was wide separation of the nipples, and syndactyly of the middle three toes of both feet. The genitalia were normal for a prepubertal female, and there was no development of breasts or pubic and axillary hair.

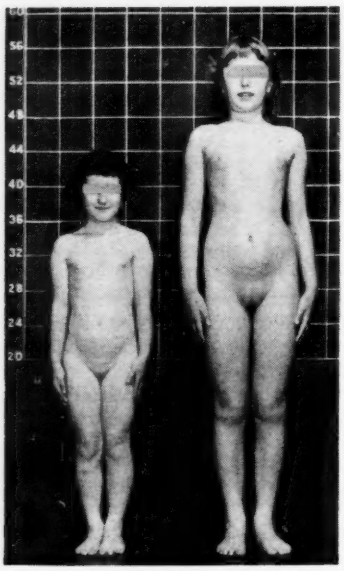


Fig. 1—The first patient (left), with a normal control of the same age.

Radiological examination showed calcification above and anterior to the pituitary fossa, which was considered to be the result of the tuberculous meningitis. The estimated bone-age was 12–14 years. There was poor modelling of the phalanges and metatarsals. The metacarpals (fig. 2) were of about equal length, and a line drawn across the heads of the fourth and fifth touched the head of the third. The urinary 17-hydroxy-corticosteroids (3 to 3·4 mg. per 24 hours), 17-ketosteroids (0·7 to 1·3 mg.), and gonadotrophins (less than 5 mg. of H.M.G.24 international reference substance) were within the normal range. The serum-calcium (10·3 mg. per 100 ml.), serum-phosphorus (4·2 mg. per 100 ml.), and alkaline-phosphatase (18 K.A. units) were normal. The serum-cholesterol was 222 mg. per 100 ml., and the protein-bound iodine 4·0 μg. per 100 ml.

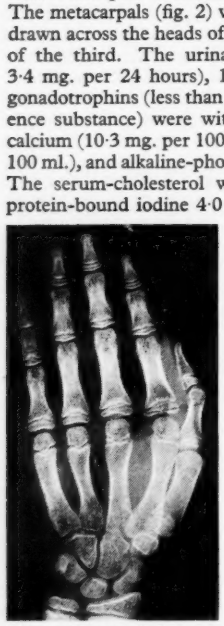


Fig. 2—X-ray of the first patient's hand, showing metacarpals of equal length.

The features of Turner's syndrome displayed by this girl are dwarfism, separation of the nipples, mental retardation, and abnormal metacarpal bones. The normal level of gonadotrophins, and slight breast enlargement observed more recently, suggest that the ovaries may be normal, but laparotomy to determine whether this is so has not been performed.

THE SECOND CASE

This girl is an only child of healthy parents, who was admitted to hospital under the care of Dr. B. S. B. Wood and Mr. V. S. Brookes on the 3rd day of life, because of vomiting. The abdomen was distended, and radiological examination showed distension of the small intestine, with gas and fluid levels, but no gas was seen beyond the ascending colon. At laparotomy, 4 days later, the jejunum was found to be distended and the lower ileum was collapsed and empty. No cause of obstruction was found, and the abdomen was closed. For the next 3 weeks she was maintained by intravenous fluids. There was no spontaneous bowel action, but good results were obtained from rectal washouts.

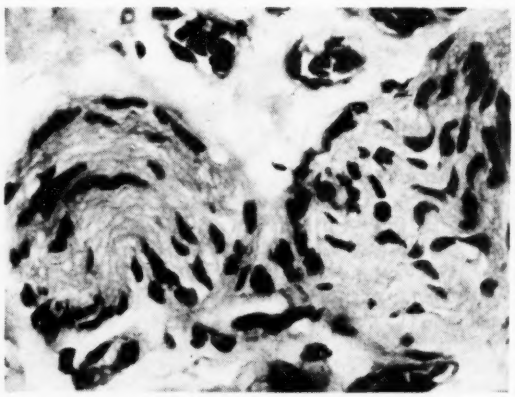


Fig. 3—Rectal biopsy: thickened nerve-trunks in Meissner's plexus. (Hæmatoxylin and eosin. ×300.)

Barium-enema showed a narrow rectosigmoid, with the calibre increasing near the level of the iliac crest. The clinical diagnosis of Hirschsprung's disease with an unusually long narrow segment was confirmed by rectal biopsy (specimen 1).

At 4 weeks a second laparotomy was performed. As before, dilatation was limited to the jejunum and upper ileum, with the rest of the bowel collapsed and empty. A transitional area of coning 2–3 cm. long was situated about 15–20 cm. from the ileocæcal junction. This segment of bowel was opened and no mechanical obstruction was found. The cæcum, terminal ileum, and a segment of distended ileum were resected (specimen 2), and the free ends of the ileum and colon were exteriorised. Later much fluid was lost from the ileostomy, and it was very difficult to maintain adequate nutrition. There was a period of obstruction from kinking of the bowel near the ileostomy, which was relieved by a third operation at which the ileostomy was refashioned and a short segment of ileum was resected (specimen 3). The child was eventually discharged at the age of 1 year, by which time she had regained her birth-weight of 7 lb. 4 oz. It is planned to carry out a formal surgical repair later.

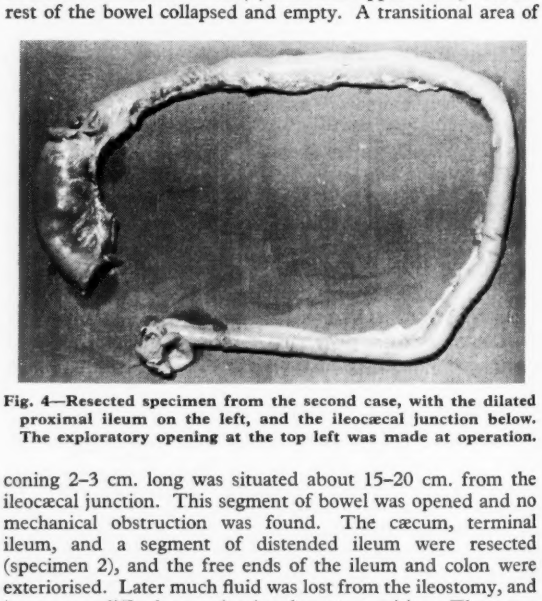


Fig. 4—Resected specimen from the second case, with the dilated proximal ileum on the left, and the ileocæcal junction below. The exploratory opening at the top left was made at operation.

Histological Examination

Specimen 1 consisted of rectal mucosa and submucosa. Meissner's plexus showed thickened nerve-trunks, and absence of ganglion cells (fig. 3).

Specimen 2 comprised 40 cm. of ileum and 1·5 cm of cæcum, with a normal appendix (fig. 4). The proximal 5 cm. was hypertrophied and dilated, the lumen being 1·3 cm. in diameter. Below this was a well-defined cone and the calibre of the lumen rapidly narrowed to 0·6 cm. beyond this point. No cause of obstruction was demonstrable. Both plexuses at the proximal end of the ileum were normal. In the coned segment ganglion cells were absent from Meissner's plexus and reduced in number in Auerbach's plexus, and the nerve-trunks were not thickened. In the cæcum both plexuses contained slightly thickened nerve-trunks, and ganglion cells were much reduced

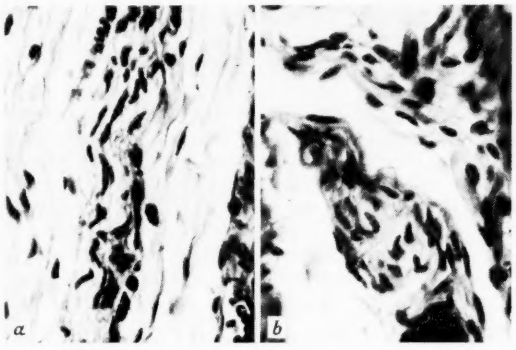


Fig. 5—Cæcum: (*a*) Meissner's plexus, and (*b*) Auerbach's plexus, showing thickened nerve-trunks. (H. & E. ×200.)

in number in Auerbach's plexus and absent from Meissner's plexus (fig. 5).

Specimen 3 consisted of two segments of thickened ileum, 1·2 and 4·0 cm. long, which showed no abnormality of either nerve-plexus.

Cytological Observations

Nuclear Sexing

The first case.—Several buccal smears, examined on three separate occasions, all showed a low proportion of chromatin-positive cells. The range was from 1 to 26%, with an average of 11%. 12% of the positive cells had double chromatin bodies (fig. 6). "Drumsticks" were seen in 1% of the polymorphonuclear leucocytes of the blood-film.

The second case.—Buccal smears examined on two separate occasions showed 5–9% of chromatin-positive cells. Double chromatin bodies were not seen. In the blood-film "drumsticks" were present in 2% of the polymorphonuclear leucocytes.

Chromosome Examination

The chromosome phenotypes of the bone-marrow and peripheral blood of the first case, but only that of the peripheral blood of the second case, were examined by the standard techniques; the results are presented in table II. Twenty mitotic plates from the first case, and fifteen from the second, were selected for detailed analysis (table III).

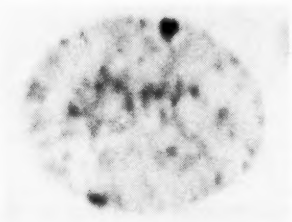


Fig. 6—Buccal smear showing double chromatin bodies. (Cresyl fast violet. ×750.)

Both cases show monosomy and trisomy involving the X chromosome or an autosome of similar size and morphology (nos. 6, 7, or 8). The low proportion of chromatin-positive cells in the buccal smears indicates that the monosomy probably involves the X chromosome, and the double chromatin bodies in the first case suggest that the trisomy also involves the X chromosome. This confirmation of the exact identity of the trisomy is lacking in the second case, but the presence of one anomaly of the X chromosome suggests that the trisomy also involves this chromosome.

TABLE I—HUMAN SEX-CHROMOSOME MOSAICS

Clinical condition	Phenotype	Chromosome constitution	Reference
Klinefelter ..	Male	XXY/XX	Ford et al. (1959a) Hayward (1960)
		XY/XXY	Tough et al. (1961)
Turner's	Female	XX/XO	Ford (1960)
		XXX/XO	Jacobs et al. (1960)
Intersex	Female	XY/XO	Blank et al. (1960)
True hermaphrodite	?	XY/XO	Hirschhorn et al. (1960)

Discussion

The successful identification of mosaicism depends primarily on awareness of its possible existence, together with adequate sampling of the body tissues for cell culture and chromosome analysis. Mosaicism can be suspected when a low proportion of chromatin-positive cells is found in the buccal smear. Both our cases were detected in this way, and the additional finding of double chromatin bodies in the first case suggested that XXX formed part of the sex-chromosome constitution. Cytological examination of a single tissue, such as the marrow sample in the first case, may be misleading if the significance of the unusual appearance of the buccal smear is not appreciated.

Deductions regarding the possible mechanism of origin of mosaicism presuppose that its full extent has been determined in the subject being investigated. All the possible variants, as well as several types of non-mosaic aneuploidy, are thought to arise by mitotic non-disjunction. The resultant cell pattern indicates the time in embryogenesis when non-disjunction probably occurred. The possible factors governing mitotic non-disjunction and its relation to mosaicism have been discussed elsewhere (Ford et al. 1959a, Hayward 1960). In all instances differential survival of the various cell types may modify the original pattern. For example, cells without an X chromosome have never been recovered and are presumably inviable. Additional factors are concerned in the XO/XY and XXY/XX conditions (table I). Both involve loss of a Y chromosome, which may be due to its smallness, or to preferential survival of an XY or XX cell as opposed to an XYY or XXYY cell. The possible results of non-disjunction during the first or later cleavage divisions in normal (XX and XY) and abnormal (XO and XXY zygotes are shown in table IV (see also Hayward et al. 1961). The

TABLE II—CHROMOSOME PHENOTYPES

Case	Tissue	Chromosome no.			No. of cells examined
		45	46	47	
First	Bone-marrow	25	0	0	25
	Blood	34	12	11	57
Second	Blood	27	13	7	47

TABLE III—ANALYSIS OF MITOTIC PLATES

Case	Tissue	Chromosome no.	No. of cells examined	Sex chromosomes
First	Bone-marrow	45	5	XO
	Blood	45	8	XO (fig. 7*a*)
	,,	46	4	XX (,, 7*b*)
	,,	47	3	XXX (,, 7*c*)
Second ..	,,	45	9	XO
	,,	46	4	XX
	,,	47	2	XXX

two cases now reported have evidence of non-disjunction at the second or subsequent cleavage divisions.

Since the first cytological observations in Turner's syndrome showed an association with a chromatin-negative buccal smear (Wilkins et al. 1954) and with an XO sex-chromosome constitution (Ford et al. 1959b), several exceptions have been recorded. Bishop et al. (1960) and Ford (1960) have described chromatin-positive cases, and those of Ford were found to be XO/XX mosaics. Examples of otherwise typical Turner's syndrome have been reported in chromatin-negative XO fertile females (Bahner et al. 1960, Stewart 1960), and in chromatin-negative XY males (Chu et al. 1961). Two chromatin-positive females, tentatively diagnosed as having Turner's syndrome, were found to have XX sex chromosomes (Fraccaro et al. 1960).*

The somatic manifestations of Turner's syndrome vary widely, even in the presence of an XO chromosomal constitution. It is still convenient to retain this eponym for all variants of the syndrome, including those without gonadal dysgenesis and the classical XO chromosomal complement. A rational genetic hypothesis to account for the ætiology of Turner's syndrome must take into consideration these unusual variants, and also the triple mosaicism featured in our first case. Those females with XX, and males with XY, constitution make untenable the hypothesis that the syndrome is due simply to absence of the X chromosome. The most attractive explanation is that the syndrome in chromatin-negative XO females is due to unbalance, as a result of deficiency of an X chromosome. In these terms the much rarer condition in chromatin-negative XY males, and the even rarer possibility of chromatin-positive XX females, must be due to an X-linked recessive mutation. The basic abnormality common to these different types is therefore a reduction in the active gene complement of the X chromosome, which is normally required to preserve the balance between the sex chromosomes and the autosomes.

Variations in the clinical expression of Turner's syndrome may result from genic variability of the X chromosome, together with variations in the whole genic background. Mosaicism of sex chromosomes may also have this effect, but here one might expect a regional or system-linked variation in expression. There is no adequate information as to whether mosaicism in Turner's syndrome is generally associated with incomplete clinical expression of the condition, but this seems to be so in our first case.

Our second case was examined cytologically because Hirschsprung's disease is more common in males than females (Bodian et al. 1951). During the past 4 years in this hospital thirteen (72%) of the eighteen pathologically verified cases have been male. The abnormal chromosome constitution reported here may possibly be unrelated to the clinical condition (Hayward and Bower 1961), because we have since examined two further females with verified Hirschsprung's disease who both proved to be chromatin-positive, with an XX sex-chromosome constitution.

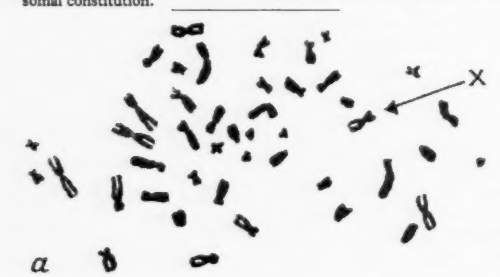
There is good evidence that Hirschsprung's disease is genetically determined, but family studies (Bodian et al. 1951) indicate that it is not under simple gene control. The predominance in males suggests the possibility of X-linked or sex-limited inheritance. Thus, in a hemizygous XO female, a recessive gene could express itself as in a heterozygous XY male. The XO component of the mosaic described may therefore be significant in this direction. Alternatively the excess of affected males may be the result of developmental reactions induced by the specific genotype taking a different course in males and females.

TABLE IV—PATTERNS OF SEX-CHROMOSOME ANEUPLOIDY PRODUCED BY MITOTIC NON-DISJUNCTION

Zygote	Non-disjunction at 1st cleavage division	Reference	Non-disjunction at 2nd or subsequent cleavage division	Reference
XY	XXYY	Muldal and Ockey (1960)	XY/XXYY	..
	XXY/YO	..	XY/XXY/YO	Tough et al. (1961)
	XYY/XO	..	XY/XYY/XO	..
XX	XXX/XO	Jacobs et al. (1960)	XXX/XX/XO	Present report
	XXXX	Carr et al. (1960)	XXXX/XX	..
XXY	XXXXYY	..	XXXXYY/XXY	..
	XXXY/XY	..	XXXY/XY/XXY	..
	XXXX/YO	..	XXXX/YO/XXY	..
	XXYY/XX	..	XXYY/XX/XXY	..
XO	XX/OO	..	XX/XO	Ford (1960)

The OO and YO components are probably inviable and will alter the resultant pattern of mosaicism (cf. table I).

*Jacobs et al. (1961) have reported five patients with mosaicism (XO/XY, XO/XX, XO/XXX, XO/XYY, and XO/YY) and hypoplastic external genitalia in a series of women with primary amenorrhœa. Four of them had hypoplastic "streak" ovaries. The gonads of the fifth patient were not examined; she had webbing of the neck and an XO/XYY chromosomal constitution.



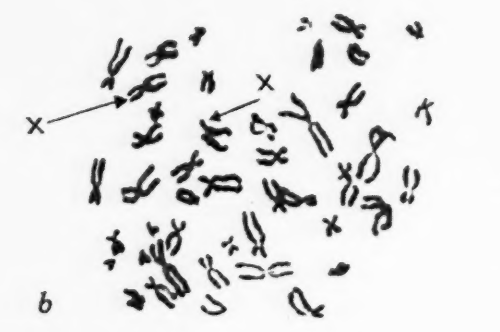


Fig. 7—Mitotic cells with (*a*) 45 chromosomes (XO); (*b*) 46 chromosomes (XX); and (*c*) 47 chromosomes (XXX).

Hirschsprung's disease, with a long aganglionic segment involving the whole colon, is not only rare but is more common in females. No other cases with long segments involving the whole colon have been encountered in this hospital, whilst six of the eight such cases reported by Dorman (1957) and Bowden et al. (1957) were female. It may be that such patients are homozygous XX, and that the unusually extensive intestinal lesion results from two doses of the abnormal gene. In these circumstances the sex-chromosome mosaicism in our patient may not be directly related to the intestinal anomaly. More complete genetic information is clearly required in Hirschsprung's disease, and in particular, female cases, especially those with long aganglionic segments, merit cytological investigation.

Summary

Triple mosaicism (XO/XX/XXX) is described in a patient with Turner's syndrome and in one with Hirschsprung's disease.

The significance of the chromosomal anomaly is related to the findings in buccal smears, to the effects of non-disjunction during early cleavage divisions of the embryo, and to the variable clinical manifestations of the two syndromes.

We are grateful to Prof. K. Mather and Dr. B. John for their helpful guidance and criticism; and to Prof. D. V. Hubble, Dr. B. S. B. Wood, and Mr. V. S. Brookes who instigated the investigations in these two patients.

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CHROMOSOMAL ABNORMALITIES IN A CHILD WITH A CONVULSIVE DISORDER

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SINCE the development of new techniques for examining chromosomes (Makino and Nishimura 1952, Hsu and Pomerat 1953, Ford and Hamerton 1956) and the establishment of a standard nomenclature (Denver classification 1960), chromosomal abnormalities have been associated with leukæmia, mongolism, and multiple congenital anomalies (Ford et al. 1959, Polani et al. 1960, Makino et al. 1960, Patau et al. 1960, Nowell and Hungerford 1960).

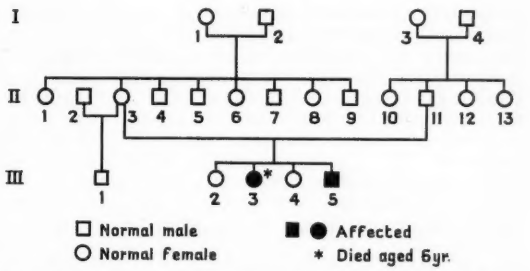


Fig. 1—Pedigree of a family group showing degenerative disease of the central nervous system in a brother and a sister.

This report concerns the chromosomal findings in a 6-year-old child with a convulsive disorder. Leucocytes from peripheral blood cultivated by a slight modification of Nowell and Hungerford's method (1960, and Hungerford et al. 1959) were examined to determine modal values and karyotypes.

Clinical Records

The pedigree represented in fig. 1, which depicts three generations, was established by personal interview with the parents of the affected children and by examination of medical records. Careful questioning failed to disclose any familial disease or neurological disturbance other than that of the propositus (III, 5) and his sister (III, 3).

Fig. 2—The boy with a convulsive disorder (III, 5): (*a*) at 3 years 5 months, and (*b*) at 4 years 10 months.

The sister (fig. 1; III, 3) was born in 1948, a full-term 6-lb. child—the second of four children of a mother aged 26 and a father aged 27. Pregnancy, delivery, and postnatal period were all uneventful. The mother did not recall details of development, but felt that the child progressed as quickly as her other children.

At 3 years the child was admitted to a hospital after a grand-mal seizure. Physical examination was normal, but she was lethargic. Laboratory studies (including lumbar puncture, urine analysis, fasting blood-sugar, and serum calcium and phosphorus levels) were within normal limits. The skull films, pneumoencephalogram, and electroencephalogram were normal.

During the next year her convulsions became more frequent and lasted longer, and her mental retardation became more evident. At $4^1/_2$ she was seen at the Mayo Clinic where physical examination disclosed a chronically ill and unresponsive child, unable to sit, walk, or talk. Skull films and a pneumoencephalogram were again normal. The electro-

encephalogram now showed generalised dysrhythmia and extreme sensitivity to light stimulus.

Convulsions and retardation continued until the age of 6 when she died after a respiratory infection. Necropsy was not performed.

The propositus (fig. 1/III, 5 and fig. 2).—A full-term 7-lb. boy was born in 1955—the last of four children of a mother aged 33 and a father aged 34. Pregnancy, delivery, and postnatal period were uneventful. The child developed normally, sitting unsupported at 5 months, walking at 10 months, and saying his first words at 1 year. There were no episodes of high fever, delirium, or serious infections.

At the age of 3 he was taken to a hospital after a 15-minute generalised convulsion. Physical examination at that time was normal, and he was afebrile. Routine laboratory tests and skull films were within normal limits, and an electroencephalogram was consistent with severe diffuse cortical disturbance. The child was diagnosed as having an idiopathic petit-mal convulsive disorder, and anticonvulsive medication was begun. Seizures continued despite trial of various drug combinations.

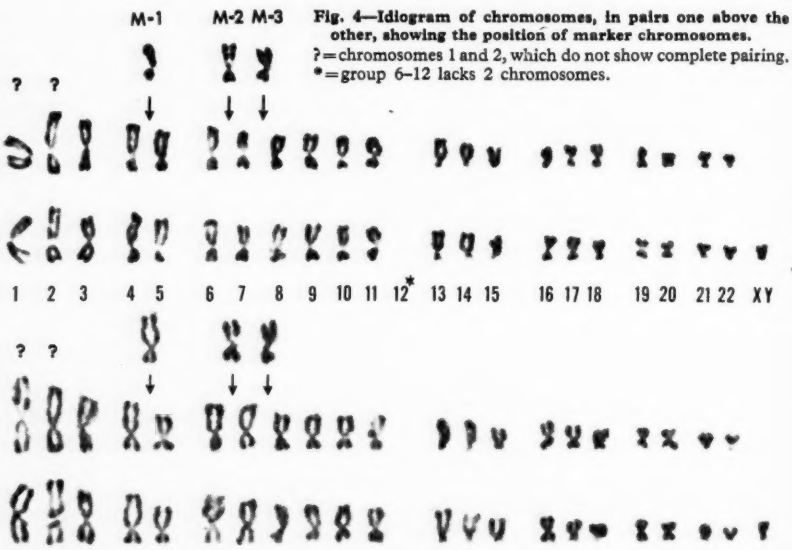


Fig. 4—Idiogram of chromosomes, in pairs one above the other, showing the position of marker chromosomes.
?=chromosomes 1 and 2, which do not show complete pairing.
*=group 6–12 lacks 2 chromosomes.

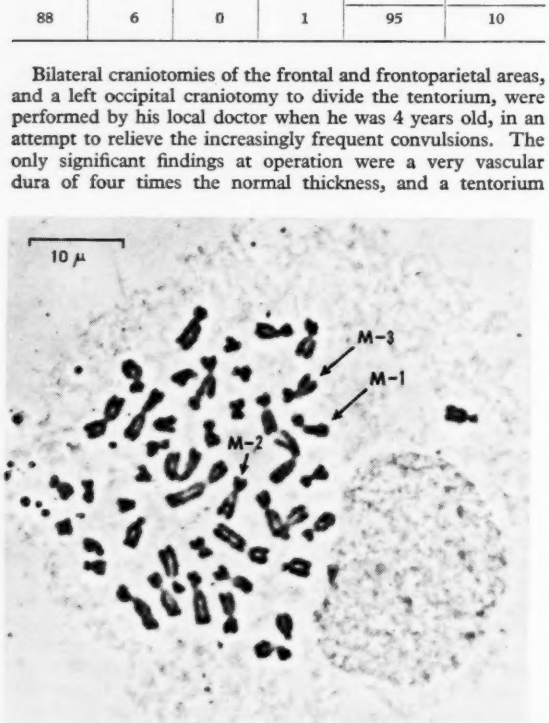
TABLE I—CHROMOSOMAL COUNTS OF CELLS CULTIVATED FROM PERIPHERAL LEUCOCYTES OF A CHILD WITH A CONVULSIVE DISORDER

Chromosome counts				Total cells	
46	47	48	49	Counted	Analysed
88	6	0	1	95	10

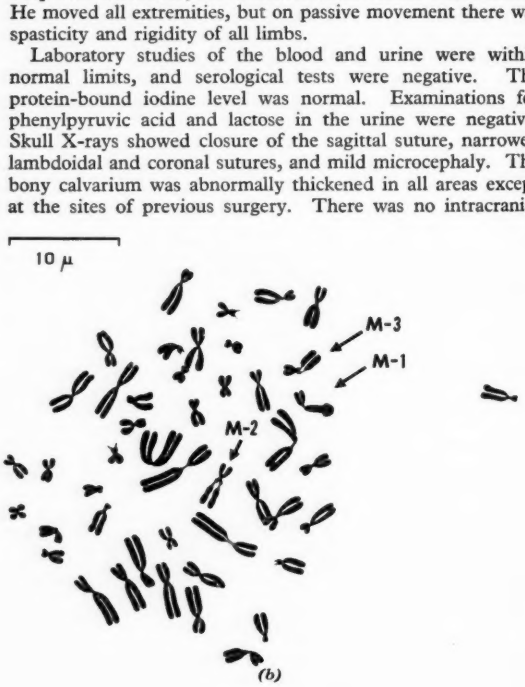
Bilateral craniotomies of the frontal and frontoparietal areas, and a left occipital craniotomy to divide the tentorium, were performed by his local doctor when he was 4 years old, in an attempt to relieve the increasingly frequent convulsions. The only significant findings at operation were a very vascular dura of four times the normal thickness, and a tentorium three times normal thickness. Horizontal brow X-rays showed that the frontal horns were enlarged to twice normal size. There was no objective change in his condition after surgery.

Examination in the Orthopædic Hospital in Los Angeles a year later disclosed considerable progression of his disease. He was lethargic, responding to painful stimuli only. The cranial nerves were intact. Cerebellar function, sensory responses, and mental state were not tested. Hoffman's sign was positive. Bilateral positive Babinski's sign, exaggerated deep tendon-reflexes, and sustained ankle clonus were elicited. He moved all extremities, but on passive movement there was spasticity and rigidity of all limbs.

Laboratory studies of the blood and urine were within normal limits, and serological tests were negative. The protein-bound iodine level was normal. Examinations for phenylpyruvic acid and lactose in the urine were negative. Skull X-rays showed closure of the sagittal suture, narrowed lambdoidal and coronal sutures, and mild microcephaly. The bony calvarium was abnormally thickened in all areas except at the sites of previous surgery. There was no intracranial



(a)



(b)

Fig. 3—Metaphase of leucocyte.
Arrows show 3 marker chromosomes designated as M-1, M-2, and M-3. (*a*) Photomicrograph, and (*b*) camera-lucida drawing.

calcification, or evidence of increased pressure. The sella turcica was normal. X-rays of the pelvis and hips were normal.

Cytological Observations

Leucocytes from the boy's heparinised peripheral blood, treated with phytohæmagglutinin M (' Difco '), were processed according to the method of Ohnuki et al. (1961). Chromosome-counts, summarised in table I, showed a modal value of 46. Of ninety-five cells examined, six had 47 and one had 49 chromosomes. The determination of the karyotype was based on the microscopic examination of ninety-five well-spread cells, with the aid of simple sketches, camera-lucida drawings, and enlarged photomicrographs. Terminology and numeration followed the standard system of nomenclature.

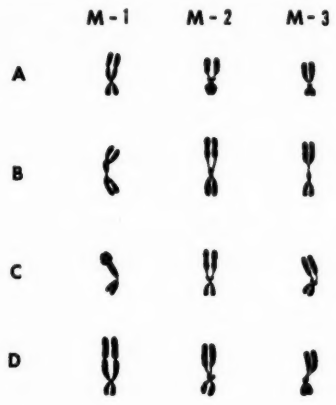


Fig. 5—Camera-lucida drawing of the 3 marker chromosomes in four different cells (A-D).

Detailed analysis of ten cells disclosed the three marker chromosomes shown in figs. 3*a* and *b*, which are designated M-1, M-2, and M-3. Each had a submedian centromere and a secondary constriction of its long arm. M-1 fell between chromosomes 4 and 5 in length (fig. 4). M-2 and M-3 fitted between chromosomes 6 and 7, and 7 and 8 respectively (fig. 5).

The short part of M-2 beyond the secondary constriction resembled chromosome 18 or 21 in shape, but it was longer than chromosome 21 and shorter than 18 (table II). The short part of M-3 corresponded to chromosome 21 or 22 in shape. Its size was nearly identical with chromosome 21.

Table III summarises the number of cells classified by the presence of markers. Of ninety-five metaphases examined, all three types of markers were clearly observed in thirty-seven cells. No identifiable marker was found in twenty-three cells. These observations suggest the occurrence of a mosaic; but in all well-spread cells it was not difficult to identify three markers. These could not be distinguished reliably when the chromosomes were somewhat condensed by treatment with colchicine, (Sasaki 1961) or when they overlapped at the level of the centromere.

No complete pairs of chromosomes 1 and 2 were observed. Because chromosomes 1 and 2 in the idiograms shown in fig. 4 were arranged arbitrarily according to their shape, one element of each pair is smaller than the other. Of the 14 chromosomes of pairs 6–12 which are normally present, 2 were missing. Chromosomes of groups 4–5, 13–15, 16–18, 19–20, and 21–22 seemed to correspond exactly with those of the standard idiogram. The acrocentric chromosomes of group 13–15 were clearly observed in nearly all cells; and the shortest 5 acrocentric chromosomes, including Y, were distinguished in all metaphases. It was difficult to identify the X-chromosome in this abnormal karyotype pattern, but we postulated that it might correspond to M-2 because of length and arm ratio.

TABLE II—LENGTH (IN μ) OF CHROMOSOMES 18, 21, AND 22, AND OF THE SHORT PARTS OF M-2 AND M-3 BEYOND THE SECONDARY CONSTRICTION

Cell no.	Chromosomes no.				
	18	M-2	21	M-3	22
1	2·5	2·1	1·8	1·8	1·6
2	2·1	2·1	1·8	1·8	1·4
3	2·0	1·9	1·6	1·7	1·6
4	2·4	2·8	1·8	2·4	1·6
5	2·3	1·9	1·7	1·7	1·5
6	2·8	2·3	1·7	1·7	1·6
7	1·9	1·4	1·4	1·4	1·2

Measurement was made from chromosomes of the enlarged photomicrographs. Length of chromosomes 18, 21, and 22 shows average of each pair. Markers of cell no. 4 all showed elongated form by some unknown factors. Because chromosomes of cell no. 7 showed the condensed shape by the effect of colchicine, the difference between M-2 and M-3 was not identifiable.

Discussion

Although many papers have appeared recently, associating atypical karyotypes with congenital abnormalities, few reports deal with chromosomes exhibiting secondary constrictions in relation to such diseases. The boy described in this study had three such abnormal chromosomes.

Polani et al. (1960), Penrose et al. (1960), and Carter et al. (1960) found abnormal chromosomes produced by reciprocal translocation between 2 acrocentric chromosome groups (13–15 and 21–22) in the case of mongoloid children with 46 chromosomes and their relatives. Other cases which were caused by fusion or translocation have been described recently (Bavin et al. 1961, Book et al. 1961, Cooper and Hirschhorn 1961, Hirschhorn and Cooper 1961)

The morphology of the short parts of M-2 and M-3 beyond the secondary constrictions corresponds to chromosomes 18, 21, and 22, and especially that of M-3 which exactly resembles the pattern of chromosome 21. It is tempting to speculate that one of this child's ancestors might have had a trisome of chromosome 21, one of which translocated with some other autosomes to form M-3. Clinical studies, however, failed to show any characteristics of mongolism; in this there are 47 chromosomes, including trisomy of chromosome 21, or 46 chromosomes with a marker chromosome derived from reciprocal translocation between group 13–15 and one of chromosome 21 (Polani et al. 1960, Makino et al. 1960, Penrose et al. 1960, Carter et al. 1960, Böök et al. 1961).

TABLE III—THE NUMBER OF CELLS CLASSIFIED BY THE PRESENCE OF IDENTIFIABLE MARKER CHROMOSOMES

Marker chromosomes	—	M-1	M-2	M-3	M-1 M-2	M-1 M-3	M-2 M-3	M-1 M-2 M-3	Total
Cell counts	23	8	2	4	4	15	2	37	95
Totals ..	23	14			21			37	95

The marker chromosomes may have resulted from translocations between groups 13–15 and 21–22. All cells which could be clearly observed, however, showed the shortest 5 chromosomes and 6 of group 13–15.

Only 12 of the 14 medium-sized chromosomes with submedian centromeres in group 6–12 were found. Moreover, elements of chromosome pairs 1 and 2 did not show complete pairing. It is possible, therefore, that the three markers may have been derived from the elements of groups 1–3 and 6–12. It is unlikely that the child's anticonvulsant therapy would cause breakage of definite chromosomes at identical locations.

As shown in the pedigree (fig. 1), this child had a sister (III, 3) with a similar disease of the central nervous system. If we could observe the chromosomes of his other sisters, his parents, and his grandparents, we might discover more about the origin of these abnormalities and the mechanism of translocation.

Summary

The chromosomes of leucocytes cultivated from a child with a convulsive disorder have been studied. The modal value was 46. The karyotype showed three marker chromosomes characterised by secondary constrictions.

Detailed analysis shows that these abnormal chromosomes might have been produced by translocations between elements of chromosome 1 or 2, and those of group 6–12.

A debt of gratitude is due to Dr. Robert H. Pudenz for calling our attention to this child and for providing the clinical data; and to Dr. C. M. Pomerat for encouragement and indispensable aid with the manuscript. Mr. C. George Lefeber and Mr. Robert Olson prepared the photographs. Mr. Charles Raiborn, Jr., was reponsible for the preparation of the culture media.

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MUSHROOM POISONING

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THE highly poisonous fungus, *Amanita phalloides*, and the common field mushroom, *Agaricus campestris*, are not easily distinguishable from one another. The numerous folk-lore tests, such as turning a silver spoon black, which have been relied on for many centuries, are completely fallacious and dangerously misleading. *Amanita phalloides* has a pleasant taste, and a single fungus contains enough poison to kill an adult (Wieland and Wieland 1959). Fungus poisoning is consequently common in some parts of the world. Its comparative rarity in this country is presumably due to the British reluctance to go out and harvest edible fungi (Elliott 1960); for *Amanita phalloides* is not uncommon in Britain, especially in woods and adjoining pastures in late summer and autumn. Other poisonous fungi are relatively uncommon, comprising only 20 of the 2000 species found in Great Britain (Ramsbottom 1953).

The Registrar General's reports list 38 fatal cases in England and Wales for the years 1921–49, since when it has not been listed separately. No cases have been reported in the British literature since 1949. The incidence in other countries, especially in central Europe, is much greater. Ford (1923) collected 990 cases from the French literature, and the incidence in Germany has been estimated at 200 per annum (Lewes 1948). The overall mortality-rate is difficult to estimate, partly because certain identification of the responsible fungus is virtually impossible after ingestion. When the fungus is *Amanita phalloides*, the mortality is high; Neuhann (1933) cited previous series with mortality-rates from 33 to 75%.

More than a century of investigation, mainly in Germany and France, has led to the isolation of five crystalline toxins from *Amanita phalloides* (α, β, and γ amanitin, phalloin, and phalloidin) and the almost complete description of their structural formulæ. The metabolic effects of administering the whole fungus or the pure toxins to laboratory animals, and the clinical and pathological features of poisoning in man, have also been intensively studied (see Wieland and Wieland 1959). Unfortunately the susceptibility of different animals to the orally administered fungus varies widely, and pure toxins do not reproduce all the features of poisoning by the intact fungus. The results of experimental studies are therefore difficult to apply to man. Human cases occur sporadically and are seldom diagnosed early. It is therefore not surprising that, of the many therapeutic measures which have been proposed, none has been submitted to an adequate controlled trial, and the literature abounds with contradictory reports of their value.

We report here a recent severe case in this country which illustrates some of the problems of diagnosis and treatment.

Case-record

A 50-year-old farmer was admitted to the Cumberland Infirmary, Carlisle, on Oct. 10, 1959. He complained of pain in the right hypochondrium and jaundice, and acute cholecystitis was tentatively diagnosed. The following day he had a major epileptic fit and oliguria was noted. The initial diagnosis was revised, and among the possibilities suggested was mushroom poisoning. The relatives were questioned again.

Until three months previously the family had lived on a farm where they frequently gathered mushrooms. They had then moved to a more prosperous farm containing some birch scrub where the patient had collected a meal of mushrooms, including some from a copse. Nothing strange was noticed about the mushrooms; and a large stew had been eaten by the patient, his wife, and his nephew on Oct. 5, 1959. The wife suffered no ill effects but the nephew vomited several times that evening and felt unwell for two or three days. His "liver-function tests" were estimated on the thirteenth day, and slight abnormalities were noted. By this time he was feeling well and he has had no symptoms since.

About six hours after the meal the patient developed profuse watery diarrhœa which persisted for forty-eight hours. On the third day he developed upper abdominal pain and vomiting, and on the fifth day he became jaundiced. It was at this stage that he was admitted to hospital. His condition rapidly deteriorated. After the fit, his level of consciousness fluctuated. He became extremely irritable and swore at his medical attendants when disturbed. Spontaneous clonic twitching of

the muscles of his limbs and face appeared. Within forty-eight hours he was anuric, and he was therefore transferred to the artificial-kidney unit, Royal Victoria Infirmary, on the eighth day.

Examination

On admission the patient was drowsy and most of the time completely inaccessible. Violent involuntary movements were present at rest; when he was disturbed these were greatly accentuated and became athetoid; attempted purposeful movement caused an increase in the jerking, and he sprayed himself with water while attempting to drink. A petechial rash appeared over the shoulders, but he was no longer clinically jaundiced. The blood-urea was 296 mg. per 100 ml.; plasma sodium 138 mEq. per litre, potassium 4·8 mEq. per litre, bicarbonate 19 mEq. per litre; blood-sugar 116 mg. per 100 ml.; serum-bilirubin 0·6 mg. per 100 ml.; flocculation tests negative; serum glutamic oxaloacetic transaminase 112, glutamic pyruvic transaminase 37 Sigma Frankel units; serum albumin 4·5 g. per 100 ml., globulin 1·9 g. per 100 ml.; serum calcium 8·2 mg. per 100 ml., phosphate 6·2 mg. per 100 ml.; Hb 11·3 g. per 100 ml., white blood-cells 13,400 per c. mm. (85% polymorphs), platelets 400,000 per c. mm. Haptoglobin was present in the plasma. The electrocardiogram was normal.

Treatment

Serum antiphalloidien was obtained from the Pasteur Institute, Paris, and 65 ml. was administered intramuscularly over 12 hours. Treatment was otherwise symptomatic.

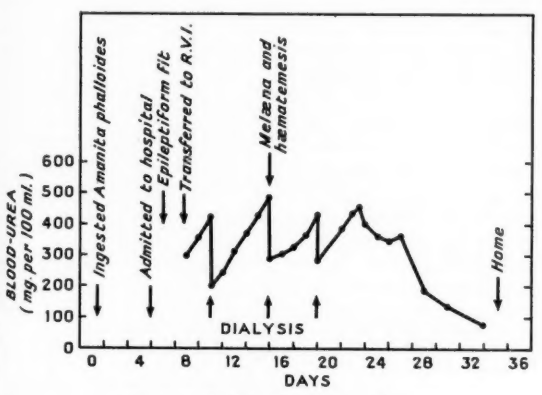

Fig. 1—Daily blood-urea estimations.

During the period of oliguria the patient was given 500 ml. of dextrose daily (at first rectally, later orally) until the sixteenth day, after which he was able to take a protein-restricted diet (Elliott et al. 1960). Six-hour hæmodialyses were performed with an Allwal artificial kidney on the tenth, fifteenth, and nineteenth days (fig. 1). Hæmatemesis and melæna before the second dialysis responded to transfusion.

An unexpected improvement occurred during the first hæmodialysis; muscle twitching ceased abruptly. However, the patient remained confused and restless with severe skin irritation. The following day he could drink, and two days later he could repeat simple words. He remained drowsy, confused, and incontinent and made no spontaneous attempt at conversation until the twenty-sixth day when he asked for a glass of beer. Rapid recovery of mental function then took place and within a fortnight he was walking, talking, and feeding himself. His mental state was not yet normal, however, and the electroencephalogram showed rather low-amplitude slow activity much of it of delta frequency, compatible with a delirium. His intelligence quotient (I.Q.) by the verbal test of the Weschler scale was 92 and by the performance test 97. His blood-urea was 36 mg. per 100 ml., and liver function tests were essentially normal. His Hb was 8·8 g. per 100 ml., and he still had infections of the skin and urinary tract with " hospital organisms ". At this stage he was allowed home.

Progress

He was readmitted for assessment five months later. There were no stigmata of liver disease. The serum-globulin remained elevated, and the zinc-sulphate turbidity was 18 Kunkel units. Other flocculation tests, serum bilirubin, alkaline phosphatase, transaminases, and electrolytes, and bromsulphthalein retention were normal; liver biopsy showed a normal histological appearance.

The plasma-urea was 26 mg. per 100 ml., maximum urea clearance 47 ml. per min. and creatinine clearance 77 ml. per min., but midstream urine still contained organisms resistant to all antibiotics. Hb, white-blood-cell count, and platelets were normal.

The patient's I.Q. had risen to 109 on the verbal test and 108 on the performance test of the Weschler scale, and the electroencephalogram had returned to normal. He was by now feeling well and was running his 400-acre farm. He has been seen at intervals since and remains well (May, 1961).

Diagnosis

Discussion

The case presented in hospital as one of hepatorenal failure of unknown origin. The cause would have remained obscure had not the pathologist recalled a conversation with a colleague who had seen a case of mushroom poisoning in East Anglia several years previously. This recollection prompted the questioning of the relatives, who then gave the history of ingestion of mushroom stew, and the general practitioner confirmed that *Amanita phalloides* could indeed be found in the vicinity of the patient's farm. Presumably some similar cases remain undiagnosed since the latent period before the onset of symptoms directs attention away from the mushrooms. Moreover there is no pathognomonic feature at necropsy to distinguish the condition from other forms of hepatic and renal failure once the mushrooms have been digested or passed. Diagnosis in this case was based on the typical combination of initial latent period, severe gastroenteritis, hepatorenal failure, muscular twitching, stupor, and convulsion. The occurrence of severe poisoning, mild poisoning, and asymptomatic cases among people who have ingested the same meal is well recognised and is presumably accounted for by the inclusion of only one or two poisonous fungi in a batch of edible mushrooms.

Treatment

The therapeutic measures that have been suggested in the past include:

(1) *Gastric and colonic lavage* during the stage of gastroenteritis, to remove undigested fungi, and the administration of charcoal to adsorb the toxins. These measures are apparently worth-while as late as forty-eight hours after the onset of symptoms since the fungi are very slowly digested (Neuhann 1933).

(2) *Administration of sodium chloride, with or without adrenal steroids* (Cheymol and Pfeiffer 1949). This is presumably a symptomatic measure and would now be included in the usual treatment of a patient with severe gastroenteritis.

(3) *Oral administration of an antidote*, up to forty-eight hours after ingestion of the fungus. It has been observed that rabbits are susceptible to injected toxin but not to orally administered mushrooms, and that they do not develop cerebral symptoms. The administration of rabbit's stomach and brain, in the form of a sandwich, has therefore been suggested as an antidote. Good results have been claimed in experiments on cats and in two small outbreaks of human poisoning diagnosed during the stage of gastroenteritis (Limousin and Petit 1932). The efficacy of this measure has not been established, and it is presumably useless once the toxins have been absorbed from the gut.

(4) *Administration of glucose intravenously*. Most animals that die early from poisoning by the fungus of pure amanita toxins develop an early hyperglycæmia followed by hypo-

glycæmia and convulsions. The liver is progressively depleted of glycogen. There are conflicting reports on whether convulsions can be postponed and life prolonged by glucose administration (Vogt 1938, Binet and Leblanc 1953), but it is generally agreed that the depletion of liver glycogen is irreversible (Wieland et al. 1952). In the absence of any clear-cut evidence for or against its value in human cases, intravenous administration of glucose would seem reasonable until adequate amounts can be ingested.

None of these measures was applicable to our patient, in whom the disorder was diagnosed after the gastro-enteritis had subsided and when liver damage was recovering.

(5) *Administration of serum from horses immunised against injected extracts of* Amanita phalloides. This procedure has been used in France for many years and good results have been claimed in animal experiments (Dujarric de la Rivière 1925) and in the treatment of human poisoning (Rayel 1925). Wieland and Wieland (1959), after critical review of the literature, concluded: "in no instance could specific antibodies be demonstrated convincingly, least of all in the French 'serum antiphallinique'." There is some evidence that the protective effect of the serum in animal experiments is a nonspecific effect of immune horse-serum, and that anti-gasgangrene serum is equally effective (Schlossberger and Menk 1931). It has also been suggested that serum protects only against the hæmolytic toxin, phalloidin, which is unimportant in human poisoning, since it is destroyed by cooking.

In most animal experiments the antiserum has been injected at the same time as the toxin or soon after. The opportunity for early administration seldom arises in man, and we doubt whether the very late administration of the serum in our patient was responsible for recovery. It was given in hope rather than expectation of benefit, when his condition was critical.

Hæmodialysis

In mushroom poisoning hæmodialysis is obviously essential when, as in this patient, severe oliguric renal failure occurs; and on this occasion it proved life-saving. We have not been able to trace any previous reports of its use.

One interesting feature was the improvement in muscular irritability during the first dialysis; only the test dose of the serum antiphalloidien had been given at this time. The toxins of *Amanita phalloides* have molecular weights between 800 and 1100 and are known to be poorly dialysable in vitro. It is therefore unlikely that a large amount of toxin was removed during a hæmodialysis which reduced the level of blood-urea (molecular weight 60) by only 50%. Another possible explanation of the improvement is the correction of aggravating factors such as uræmia or cerebral œdema during the dialysis; but the type of involuntary movement in this patient (and in previously described cases) was quite unlike any of the usual manifestations of uræmia.

Further study of the effects of hæmodialysis is obviously required since there is no reason why a machine of larger surface area should not be used for a longer period and at an earlier stage in the disease. Under these circumstances useful quantities of fairly large molecules can be removed from the body, and it is conceivable that amanita toxins could be removed before much of the damage had been done.

Prognosis

Our patient displayed several features which are found only in severe poisoning. Convulsions and purpura are both of serious import, and no previous patient has recovered from renal failure of this degree due to fungus poisoning. Mental symptoms carry a particularly bad prognosis, and Neuhann (1933), in the most extensive review of the literature to date, stated: "the onset of psychological symptoms ushers in the end". If our assumption that attempts at neutralisation and removal of the toxins were largely unsuccessful is correct, his recovery must be attributed to the more adequate supportive therapy of acute renal failure now available.

The most encouraging feature is the virtually complete recovery of every affected organ. Enthusiastic symptomatic treatment of all the usual manifestations of fluid imbalance, hypoglycæmia, acute hepatic and renal failure, coma, and convulsions are obviously worth while even in apparently hopeless cases.

Identification of Poisonous Fungi

The terms "mushroom" and "toadstool" have no specific meaning and are used interchangeably by some mycologists; they certainly bear no relationship to whether the fungi are edible and for this reason are better avoided.

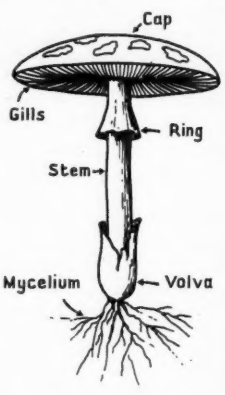

Fig. 2—*Amanita phalloides*: mature specimen.

A number of fungi can cause very unpleasant symptoms (Grossman and Malbin 1954), but it is said that all fatal cases are due to members of the genus *Amanita* (Wieland and Wieland 1959). If one can recognise this genus without fail, fungus eating becomes a much less risky pastime.

The main distinguishing feature from *Agaricus campestris*, the "common field mushroom", is the presence of the "volva". This is a membrane which surrounds the young fruiting body (the reproductive organ of the mycelium) (fig. 2). As the gills form and the stalk grows this membrane is ruptured but is left at the base of the stalk as a definite swelling. A second membrane exists which stretches from the edge of the gills to the stalk and is torn as the fungus grows to be left as a ring around the stalk—"the annulus" (fig. 3). Each feature occurs separately in other genera, but together they are found only in the genus *Amanita* and in a common dung fungus (*Panæolus schioratus*) which is unlikely to be confused with amanita.

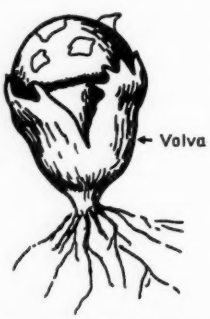

Fig. 3—*Amanita phalloides*: immature specimen.

Identification by colour is unreliable. Although the stalk and gills are white the dome of the *Amanita phalloides* is variously described as "yellowish green" (Wakefield 1958) and "greenish orange with blackish fibrils radiating from the centre" (Ramsbottom 1953), and a pure white form also occurs. The specimens we have seen in the north of England have been impossible to differentiate from *Agaricus campestris* by colour alone.

Of the individual species *Amanita phalloides* is the commonest cause of poisoning in this country. Two white species—*Amanita verna* ("the destroying angel") and *Amanita virosa*—are rare in this country but cause most of the cases of poisoning in the United States.

The safest method of obtaining mushrooms for food is to buy the cultivated variety, *Agaricus bisporus*, which in Newcastle upon Tyne accounts for above 95% of those on sale during the autumn and 100% at other times of the year.

Those who still prefer to collect fresh field fungi should avoid those growing near trees, should pick only mature specimens, and should make certain that there is no volva present. Since the volva is often obscured by soil the whole specimen should be dug up and shaken free of soil before inspection.

Summary

A patient poisoned by the fungus *Amanita phalloides* recovered completely despite jaundice, convulsion, stupor, mental change, and acute renal failure requiring repeated hæmodialysis.

The diagnosis was first suggested by Dr. J. Steven Faulds, pathologist, Cumberland Infirmary, Carlisle. Information about the presence of *Amanita phalloides* on the patient's farm was supplied by Dr. Peter Delap, Appleby, Westmorland. Dr. J. M. G. Wilson, of the Ministry of Health, London, rendered invaluable help in locating supplies of serum antiphalloidien and Prof. J. H. Burnett, Department of Botany, King's College, Newcastle upon Tyne, kindly advised on the botanical aspect.

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DETECTION OF RENAL ARTERIAL STENOSIS IN HYPERTENSION BY THE DIFFERENTIAL RENAL UPTAKE OF RADIOACTIVE RUBIDIUM

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THE classical studies of Goldblatt et al. (1934) demonstrated that hypertension could be produced in animals by constricting one or both renal arteries. A similar cause-and-effect relationship in man was not clearly recognised until the technique of aortography became established. Since then a number of cases have been reported where stenosis of a renal artery, on one or both sides, has been detected in hypertensive patients and the blood-pressure has been restored to normal levels by nephrectomy or renal arterial reconstruction (Poutasse et al. 1956, De Camp and Birchall 1958, Morris et al. 1960, Owen 1960). Aortography is not entirely devoid of risk and at present cannot be applied to screen all hypertensive patients. Selection of patients for aortography on clinical grounds appears to be unsatisfactory, although the presence of a systolic bruit over the flank is suggestive evidence of stenosis of a renal artery.

In patients with unilateral stenosis the flow of urine and excretion of sodium are reduced on the affected side (Howard et al. 1954). This test, however, requires bilateral ureteric catheterisation, and loss of some of the urine is difficult to avoid. Intravenous pyelography may show that the kidney on the affected side is smaller, and that its function is diminished; but the appearances are often normal. In an attempt to provide a semiquantitative estimate of differential renal blood-flow, the radioactivity over each kidney after intravenous injection of 'Diodrast' (injection of diodone) labelled with ^{131}I has been investigated by various groups of workers, with disappointing results owing to the high liver uptake and the complex nature of renal uptake (Dollery 1960). In the hope of devising a simple and reasonably accurate method of screening a group of hypertensive patients for renal arterial stenosis, we have investigated another type of differential renal-uptake test.

Basis of the Method

Black et al. (1955) showed that when radioactive potassium was injected intravenously it disappeared very rapidly from the blood-stream, and that this rapid clearance was due to the exchange of intravascular radiopotassium (^{42}K) with intracellular non-radioactive potassium. The kidneys were shown to be highly efficient in this respect; indeed during a single circulatory transit the exchange was virtually complete. It followed that the specific activity of each kidney after intravenous injection of ^{42}K depended on the rate of renal blood-flow, and this was confirmed experimentally (Emery et al. 1955). This blood-flow-dependent pattern of tissue uptake has been amply confirmed by other workers. Radioactive rubidium (^{86}Rb) has been shown to be distributed to the tissues in a similar fashion (Sapirstein 1958), and since its half-life (18·6 days) is much longer than that of ^{42}K, this substance is more convenient for routine clinical investigation. ^{86}Rb is a hard gamma emitter and it seemed possible that any disproportion in renal blood-flow could be detected by comparison of the radioactivity over each kidney after the intravenous injection of ^{86}Rb.

Method

The radioactivity over each kidney was detected by directional scintillation counters (Labgear type D.4133) without additional collimation, and recorded either by an automatic scaling unit (Ekco) or by two recording ratemeters (Labgear clinical ratemeter, type 14188). Both methods of estimating radioactivity were employed throughout this investigation. Immediately before each test the scintillation counters and ratemeters were adjusted to give equal count rates by comparison against a standard solution of ^{86}Rb.

With the patient prone on a firm couch, the scintillation counters were centred over the point of intersection of the erector spinæ and the 12th rib, the position being modified if an intravenous pyelogram demonstrated either kidney in an abnormal situation. The patient was instructed to maintain the position throughout the examination, which took about fifteen minutes. Background radioactivity was then measured on the scaling unit.

With the arm extended above the head, the ^{86}Rb was injected into a suitable vein in the upper limb. The dose employed varied between 10–75 μC (maximal absorbed dose 0·45 rads). The pattern of radioactive uptake from each loin was recorded by the ratemeters, until equilibrium levels were reached. The scintillation counters were then connected in turn to the

scaling unit and the count-rates determined over a period of a hundred seconds. The difference in count-rate from the two sides was estimated by subtracting the one from the other and expressing the difference as a percentage of the higher count-rate.

Results

Normals

To define the normal range and variation in count-rates 19 volunteers were studied. All were normotensive and showed no clinical evidence of renal abnormality. The mean difference in count-rates was 1%, S.D. ±8·19%. The distribution is shown in fig. 1, and from these results a normal distribution curve was derived. It was concluded that any difference in count-rate greater than 15% on the right and 17% on the left side falls outside the 95% confidence limit and suggests an abnormal tissue distribution of ^{86}Rb.

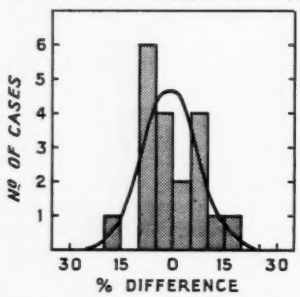

Fig. 1—The distribution of differences in count-rates following intravenous injection of ^{86}Rb is shown.

A deviation to the right or left of the zero indicates a contralateral preponderance. The calculated normal distribution curve is shown.

Nephrectomy

In a patient with carcinoma of the ureter without impairment of urine flow, the kidney was removed a few minutes after the intravenous injection of ^{86}Rb. Measurement of renal radioactivity under standard geometric conditions showed that 9% of the injected dose was present in this kidney. Since each kidney receives about 10% of the cardiac output, this finding confirms the assumption on which the method is based.

A total of 17 patients were investigated after nephrectomy. In 9 cases the left kidney had been removed and the average decrease in count-rate on the left side was 42%, S.D. ±14·4. Similarly, in 8 patients after right nephrectomy the mean decrease in count-rate was 32%, S.D. ±11·4% (fig. 2). When the count-rate differences were compared with the normal distribution curve in 16 cases the results were outside the normal range. In 1 patient the reason for a normal result was not apparent.

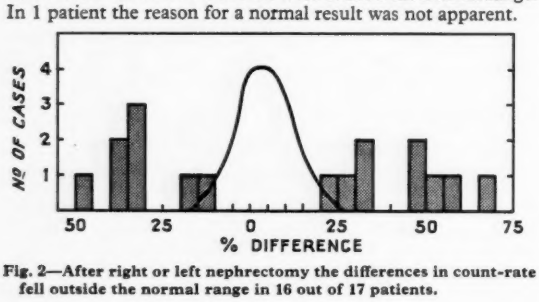

Fig. 2—After right or left nephrectomy the differences in count-rate fell outside the normal range in 16 out of 17 patients.

Hypertensive Patients

46 hypertensive patients were investigated by this technique. In most instances the patients were admitted to hospital because of the severity of the hypertension or difficulty with outpatient control. Cases referred for rubidium uptake studies were, therefore, a selected group in whom the possibility of an underlying renal mechanism for the hypertension was under consideration.

The results for the whole group of hypertensives are shown in fig. 3 in the form of a histogram with the normal distribution curve superimposed. 14 cases showed differences in count-rate outside the normal range. The relevant findings which emerged on further investigation, which included intravenous pyelography and aortography, are shown in tables I and II.

In 5 patients aortography demonstrated renal arterial stenosis —unilateral in 4, and bilateral in 1 (table I).

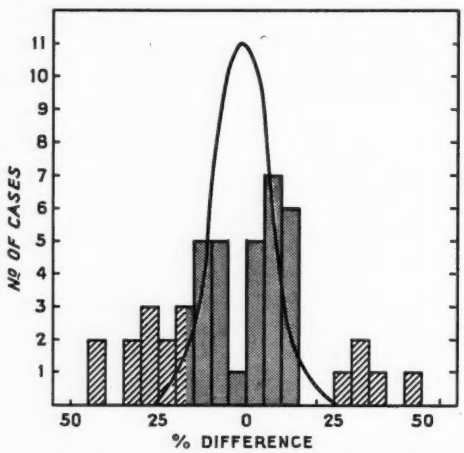

Fig. 3—The results in 46 hypertensive patients.

The shaded areas indicate the abnormal count rates detected in 14 patients. Renal arterial stenosis was later demonstrated in 5 cases, and in a further 5 cases other renal lesions were found.

In the unilateral cases the intravenous pyelogram showed satisfactory excretion of the dye on the affected side and the renal contours when compared with the contralateral kidney were not reduced.

TABLE I—RESULTS IN FIVE PROVEN EXAMPLES OF STENOSIS OF RENAL ARTERY

Age	Blood-pressure	% count-rate difference	Diagnosis
60	230/135	43	Right renal artery occluded Left renal arterial stenosis
48	230/130	31	Right renal arterial stenosis
28	190/140	30	Right renal arterial stenosis
40	150/110	33	Left renal arterial stenosis
48	240/145	40	Left renal arterial stenosis

In the patient with bilateral stenosis, the right kidney failed to function on intravenous pyelography, and aortography showed a virtually complete arterial block. At operation the right kidney was found to be grossly contracted. The left, on the other hand, functioned satisfactorily and appeared larger than normal.

Of the remaining 9 patients in whom abnormal differences in count-rates were detected, 4 have not yet had aortograms performed, although a distal aortogram in 1 of them (with peripheral vascular disease) disclosed severe atheromatous change in the lower abdominal aorta and conceivably he has a plaque at the origin of the right renal artery. Investigation of the other 5 cases disclosed significant renal disease in all—unilateral hydronephrosis with virtually complete loss of renal substance; unilateral multiple renal cysts and pyelonephritis; atypical glomerulonephritis; type II nephritis; and unilateral non-functioning kidney with a normal aortogram. The diagnoses were confirmed by operative exploration in the first 2 and

TABLE II—FINDINGS IN A FURTHER NINE HYPERTENSIVE PATIENTS IN WHOM ABNORMAL COUNT-RATE DIFFERENCES WERE DETECTED

Age	Blood-pressure	% count-rate difference	Diagnosis
17	240/150	28	Atypical glomerulonephritis
53	150/100	50	Type II nephritis
39	230/130	28	Right renal cysts and pyelonephritis
43	220/130	19	Investigations incomplete
54	190/110	20	Non-functioning right kidney Aortogram normal
37	230/140	25	Right hydronephrosis Renal atrophy
61	170/100	32	Severe aortic atheroma
45	240/145	24	Investigations incomplete
49	160/110	30	Investigations incomplete

by necropsy in the 3rd and 4th cases. The cause of the abnormal count-rates in the latter group is not obvious, though in the patient with type-II nephritis the albumin output was greater on the side with the lower count-rate.

Of the 32 hypertensive patients where the count-rate differences fell within normal limits, aortography was performed in 15. This disclosed bilateral renal arterial stenosis in 2 patients. In one the count-rate difference was 16% (i.e., upper limit of normal): the lesions in this case appeared to be symmetrical, intravenous pyelography showed equal function, and the renal outlines were identical. The other patient showed double renal arteries on both sides, with slight narrowing of the upper right and lower left renal arteries on aortography.

Intravenous pyelography in all the patients did not show gross abnormalities in any. The existing evidence therefore suggests that in the remaining cases renal arterial stenosis did not contribute to the hypertension.

Discussion

What proportion of patients with hypertension have stenosis of a renal artery it is hard to say. In the present series, narrowing of one or both renal arteries was demonstrated in 15% of patients, which is comparable to the frequency predicted by Poutasse et al. (1956).

Its relatively high prevalence in severe hypertension, together with the fact that the lesion is amenable to surgery, underlines the need for a screening test which will reveal cases requiring aortography and studies of differential renal excretion.

The ^{86}Rb-uptake test seems to be satisfactory for this purpose, since it disturbs the patient very little and is a reasonably accurate guide to the presence or absence of renal arterial stenosis. The dose of body radiation is small.

All patients in whom unilateral stenosis was demonstrated by aortography and operative exploration had previously shown grossly abnormal patterns of ^{86}Rb uptake; and a further patient with bilateral stenosis of unequal degree also showed this abnormality. On the other hand, 2 patients, of whom 1 at least had well-marked stenosis of both renal arteries, fell within the normal range. Morris et al. (1960) reported that, of 32 patients with renal arterial stenosis, in 44% this was bilateral, and the ^{86}Rb-uptake method is unlikely to demonstrate abnormalities where the lesions are of equal degree. But in many of the bilateral cases it is unequal.

Since the count-rates in the nephrectomised patients had shown a mean difference of 42% and 32% when the left and right kidneys had been removed it was surprising to encounter count-rate differences of the same order (mean difference 33%) in patients with unilateral stenosis in whom intravenous pyelography showed equal function on the two sides, without loss of renal substance. We do not yet know whether this is due to alterations in renal hæmodynamics or in the handling of ^{86}Rb by the kidney on the affected side.

Summary

Radioactive rubidium is virtually cleared from the blood passing through each kidney during a single circulatory transit, and the renal specific radioactivity therefore depends on the rate of renal blood-flow.

After intravenous injection of ^{86}Rb, radioactivity was recorded over each loin by directional scintillation counters. In normal volunteers the mean difference in count-rate from the two sides was 1%, S.D. ±8·19%. A group of patients whose left or right kidney had been removed showed a decrease in count-rate of 42% and 32% respectively.

45 hypertensive patients were investigated by this technique and in 15 cases count-rate differences outside the normal range were encountered. 5 of these patients were shown by aortography and operative exploration to have renal arterial stenosis. A further 5 were found to have unilateral loss of renal substance due to intrinsic disease such as renal cysts, 2 patients had atypical nephritis. 4 patients have not yet had aortography.

In the 32 hypertensive patients, with count-rate differences within the normal range, 1 was shown to have bilateral and symmetrical renal arterial stenosis, and 1 showed slight narrowing at the origin of the right and left renal arteries.

Where stenosis is equal on the two sides, the ^{86}Rb-uptake technique is likely to give normal results. Otherwise it appears to offer a simple, safe, and reliable means of selecting from a group of hypertensive patients those who have renal stenosis—a lesion amenable to surgery.

We are very grateful to Sir Robert Platt, Prof. Douglas Black, Dr. Henry Howat, Dr. A. Morgan Jones, and Dr. Geoffrey Wade for their close cooperation throughout this study, and to Dr. A. H. Gowenlock for the statistical analysis of the results. This work was made possible by a research grant from the board of governors of the United Manchester Hospitals and by the kindness of the Geigy Pharmaceutical Co. in providing a whole-time research scholarship for one of us (R. P. D.).

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THE ANTI-HEPARIN, ANTICOAGULANT AND HYPOTENSIVE PROPERTIES OF HEXADIMETHRINE AND PROTAMINE

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PROTAMINE sulphate was considered the anti-heparin drug of choice until Preston (1952a and b) reported that hexadimethrine bromide ('Polybrene', Abbott) was similarly useful. Both drugs have been criticised for their hypotensive and anticoagulant actions if used in excessive dosage (Anderson et al. 1960, Weiss et al. 1958). This possibility arises when they are given to neutralise heparin after a long extracorporeal bypass. Senning (1959) showed that during cardiac surgery heparin disappeared from the circulation at 1·8 i.u. per ml. per half-hour before bypass, and at 0·6 i.u. per ml. per hour during bypass.

We have therefore performed several studies in dogs to evaluate the undesirable aspects of these drugs.

The Studies

Anticoagulant Properties

The anticoagulant properties were assessed by in-vitro hexadimethrine titrations and in vivo injections of hexadimethrine. Simultaneous hexadimethrine and protamine titrations were performed to compare the anticoagulant effect of the two drugs on blood from the same animal.

* Requests for reprints to C. L. N. R.

Healthy adult dogs weighing 10 kg. were anæsthetised with pentobarbitone intravenously. A carotid artery and a peripheral vein were cannulated for pressure measurements. A cardiac catheter was manipulated into the main pulmonary artery. A plethysmographic cuff was sealed about one of the hind paws to record digital-artery pulsations. All pressure measurements were made with Stathan strain gauges on an 'Electronics for Medicine' recorder, and photographic traces were obtained.

Coagulation studies were performed by the Lee-White method. Hexadimethrine and protamine tirations were performed by Hurt's method (Hurt et al. 1956).

Control coagulation-times were recorded. Heparin 300 units per kg. body-weight was injected intravenously. Simultaneous hexadimethrine and protamine titrations were performed 30 minutes later. An hour after the heparin was given undiluted

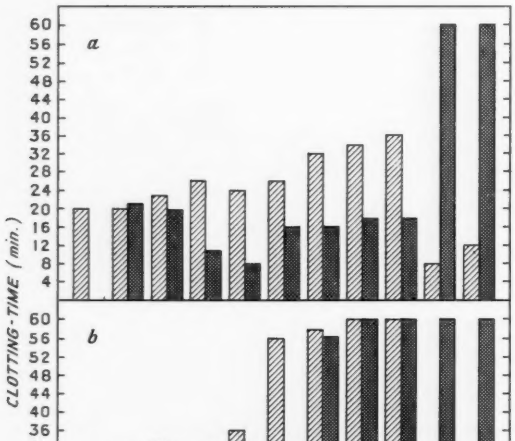

Fig. 1—The coagulation-times (in minutes) observed when non-heparinised blood (hatched columns) and heparinised blood (shaded columns) was added to tubes containing protamine (*a*) and hexadimethrine (*b*).

The height of the column indicates the time taken for clotting in each tube. Control coagulation-times are recorded on the right where blood was added to tubes containing 0·1 ml. of physiological saline.

hexadimethrine 3 mg. per kg. body-weight was injected rapidly into a subclavian vein in twelve dogs. In five dogs, protamine in similar dosage was injected intravenously. Control coagulation-times were measured 10 minutes after exhibition of the anti-heparin drug, and further samples were withdrawn 15 minutes later.

In protamine titrations, clotting-time was usually restored to control values in a slightly higher concentration tube than hexadimethrine (fig. 1). Both protamine and hexadimethrine caused prolongation of the clotting-time in higher concentrations. Above 50 μg. per ml. of blood, hexadimethrine almost invariably caused a granular agglutination of red cells which accelerates the separation of red cells from plasma. This change in a suspension of red cells is associated with the retardation of clotting observed with hexadimethrine.

In nine of twelve dogs given hexadimethrine as heparin antagonist in a ratio of hexadimethrine 1 mg. to heparin 100 units, coagulation-times were restored to normal within 10 minutes of hexadimethrine injection. In three dogs, coagulation was still prolonged for 10 minutes beyond pre-heparin

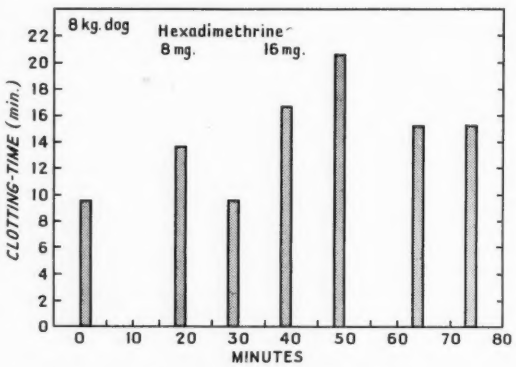

Fig. 2.—In-vivo prolongation of clotting by hexadimethrine.

The height of columns records the clotting-time of blood (in minutes) withdrawn before and after the injection of hexadimethrine in the doses indicated. The anticoagulant effect of higher doses (2 mg. per kg.) was considerably diminished after 40 minutes.

control times. Within 25 minutes of hexadimethrine injection all coagulation-times were within 2 minutes of control values. This short-lived prolongation of coagulation-times may be interpreted as due to excess hexadimethrine.

When hexadimethrine was injected into a non-heparised dog in a ratio of 1 mg. per kg. body-weight, the coagulation-time was prolonged for 15–20 minutes, and initially the tube showed granular agglutination of red cells (fig. 2). The coagulation-time was increased for a longer period when additional hexadimethrine was given in this period.

Hypotensive Properties

Vascular changes associated with slow and rapid injection of protamine and hexadimethrine were recorded. An hour after the intravenous injection of heparin 300 units per kg. body-weight, undiluted hexadimethrine 3 mg. per kg. body-weight was injected rapidly into the subclavial vein in twelve dogs; in five dogs protamine was injected in similar dosage.

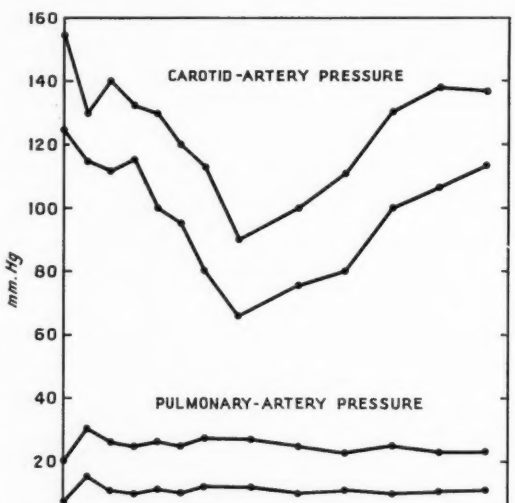

Fig. 3—Mean pressures from twelve experiments in which hexadimethrine was rapidly injected into a subclavian vein.

Transient pulmonary hypertension is succeeded by systemic hypotension. The changes are temporary and self-limiting, as observed by return toward pre-injection control values after 7 minutes.

The pressure changes in pulmonary and carotid arteries after hexadimethrine injection in twelve dogs are plotted in fig. 3 as mean systolic and diastolic pressures. The plethysmographic traces showed very slight vasodilation within the 1st minute after hexadimethrine. An immediate rise of pulmonary-artery pressure was consistently seen, and was accompanied by a temporary fall in systemic arterial pressure. At the end of 2 minutes, peripheral hypotension was maximal. Recovery was almost complete after 7 minutes. Administration of hexadimethrine alone after heparin has been neutralised has a negligible effect on the pressures recorded.

Of five dogs in which similar measurements were made after protamine injection, two showed depression of carotid-artery pressure to 40/20 mm. Hg. This hypotension persisted for 10 minutes and then slowly recovered within 40 minutes. In three dogs very little change was seen in either pulmonary or carotid artery pressures. We would emphasise that *rapid injection* is necessary to elicit the vascular changes typical of hexadimethrine, and that these changes occur only in the presence of circulating heparin; studies in five dogs showed that slow injection is innocuous in this respect.

Discussion

The undesirable anticoagulant side-effects of both protamine and hexadimethrine have been confirmed. In the case of hexadimethrine, 0·5 mg. per kg. body-weight is sufficient to increase the coagulation-time by five minutes. This level of hexadimethrine may be present if cardiac bypass has been lengthy and weight-for-weight equivalent doses of heparin antagonist have been given. Hexadimethrine titrations revealed that 5–25 μg. was sufficient to neutralise the heparin remaining 2 hours after it had been injected. When titration methods are used to estimate the coagulant required to neutralise heparin, the total body dose is calculated by multiplying the amount in the lowest concentration tube by the blood volume (85 ml. per kg. body-weight).

The vascular changes after hexadimethrine is injected rapidly into the subclavian vein are explicable either on the basis of a specific vaso-constricting effect on the pulmonary arterial bed, or as a side-effect of the respiratory stimulation observed in the 1st minute after injection. The initial depression in systemic arterial pressure is probably due to temporary decrease of left ventricular filling. The later fall of pressure is accompanied by a very slight decrease in peripheral resistance in small digital vessels, but it is probably caused by dilatation of greater degree in a vascular bed not monitored in this study. In one dog cardiogreen dye-dilution curves performed before and 2 minutes after hexadiethrine showed that cardiac output did not change significantly.

Summary

Doses of hexadimethrine bromide (' Polybrene ') and protamine sulphate, used within the therapeutic range to neutralise heparin, have been shown in dogs to have a short-term anticoagulant effect.

Acute vascular changes followed the rapid injection of hexadimethrine and protamine in the presence of circulating heparin. These changes are self-limiting, and are probably due to a decrease in total peripheral resistance.

The assistance of the National Heart Foundation of Canada is gratefully acknowledged. Abbott Laboratories, Ltd., Montreal, supplied the ' Polybrene " used in this study.

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HYPOGLYCÆMIA INDUCED BY DISODIUM ETHYLENEDIAMINE TETRA-ACETIC ACID

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DURING clinical studies on the use of chelating agents in the treatment of various cardiovascular diseases (Meltzer et al. 1960, Kitchell et al. 1961) we observed an unusual hypoglycæmic action of disodium ethylenediamine tetra-acetate (E.D.T.A.) and noted that certain diabetic patients needed less insulin after such therapy (Meltzer et al. 1961). We now describe further observations on this effect of E.D.T.A. on blood-glucose.

Observations

1. Non-diabetic subjects receiving 3·0 grammes disodium E.D.T.A. in 500 ml. normal saline solution administered intravenously in 2–3 hours, did not show any significant change in blood-glucose levels during (or after) the infusion. Ten subjects studied either fasting or after a meal showed an average change of ± 15 mg. per 100 ml.

2. When the same infusions were given to fasting diabetic patients, whose insulin was withheld, the response was usually similar to the response in the normal group, though several showed a rise in blood-glucose such as would be expected in diabetics not receiving their customary insulin.

3. When these same diabetics received the infusions *after* insulin (and breakfast) their blood-glucose fell.

We first became aware of this when a woman of 38, previously well stabilized with 25 units protamine zinc insulin (P.Z.I.) daily, had classical symptoms of hypoglycæmia 2 hours after the start of the infusion (and 3–4 hours after breakfast) on four consecutive occasions. On one of these, blood-glucose was 254 mg. per 100 ml. at the start of the infusion and 41 mg. when hypoglycæmic symptoms occurred. When the same effect was repeatedly observed in this patient and then noted in a second patient also receiving P.Z.I., our further inquiry was undertaken.

Twenty patients have been studied thus far.

4. This hypoglycæmic response is most evident in patients receiving P.Z.I. Diabetics receiving isophane (N.P.H.) insulin showed a much smaller though unequivocal) decrease of blood-sugar. Tolbutamide-treated subjects did not show it at all.

5. A decrease in blood-glucose was apparent within 1 hour of the start of the infusion and received hypoglycæmic levels within 3 hours. Patients treated with P.Z.I. often developed glycosuria that evening, and their fasting sugars next morning were higher than would be expected. Subjects receiving isophane insulin did not exhibit so distinct a pattern next morning: some showed fasting levels of 60–80 mg. per 100 ml.

6. Six stable diabetics who had long courses of these infusions of E.D.T.A.—perhaps twenty infusions in 6 weeks, for the treatment of peripheral vascular disease—all showed a gradual reduction of insulin requirements. Thus to maintain normoglycæmia a woman of 81 needed 45 units P.Z.I. before the course but only 15 units after it.

Discussion

The hypoglycæmic response seems to be related to alteration in trace-metal content induced by the chelation. Assuming that these trace metals are essential to various enzyme systems (either directly or as catalysts) it is

ELEMENTS IN μG. PER 200 ML. ALIQUOTS OF 24-HOUR-URINE SPECIMENS TAKEN BY THREE SUBJECTS (a) BEFORE, AND (b) AFTER, ADMINISTRATION OF 3 g. OF Na_2E.D.T.A. IN 500 ml. OF NORMAL SALINE SOLUTION

Subject	Pb	Zn	Cd	V	Mo	Sn	Ni
1 a	3·22	36·0	N.D. < 1·5	N.D. < 0·4	6·80	2·53	N.D. < 1
b	95·2	5200	5·10	„	3·82	1·41	1·37
2 a	N.D. < 0·4	48·8	N.D. < 1·5	„	0·82	N.D. < 0·2	N.D. < 1
b	18·2	4170	N.D. < 1·5	„	2·26	„	2·37
3 a	N.D. < 0·4	117	N.D. < 1·5	„	2·25	„	N.D. < 1
b	15·7	4200	N.D. < 1.5	„	3·95	„	1·59

N.D. = Not detectable.

reasonable to suppose that their rearrangement could influence glucose and insulin metabolism.

In our laboratory, typical excretion patterns of these metals, after administration of disodium E.D.T.A., are shown in the table. The most obvious effect is a profound zincuria.

Insulin, itself a strong chelating agent, is known to bind zinc (and other metals) present in the pancreas. The zinc-insulin chelate is important in determining the solubility of insulin, and, at the pH of blood, insulin is insoluble in the presence of excess of zinc. Insulin is thought to be stored in this zinc-complexed insoluble form in the granules of the beta cells. For insulin to become soluble the zinc-insulin bond must be broken by stronger zinc-chelators (intermediary metabolites such as oxaloacetic acid, gluthathione, or cysteine), thus allowing insulin to be physiologically active (Maske 1957).

That E.D.T.A. affects this intracellular phase seems unlikely, since it caused hypoglycæmia neither in normal subjects nor in diabetic patients who were *not* receiving insulin.

Since hypoglycæmia occurred only in insulin-treated subjects we suggest that E.D.T.A. chelated the zinc of this exogenous hormone (which had been deliberately added to control the degree of solubility), producing rapid solubility and, in turn, hypoglycæmia. Probably protamine (or other proteins) also complexed with insulin are similarly affected, which would increase the release of insulin.

Unexplained is the gradual reduction in insulin requirements following long-continued chelation therapy. This suggests some other mechanism of action.

Our work was done under a grant from the John A. Hartford Foundation. The specimens were prepared by Julia Rutman and the emission spectroscopic analyses were made by C. L. Grant.

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Preliminary Communication

TRANSMISSION BY SPLENIC CELLS OF AN AUTOIMMUNE DISEASE OCCURRING SPONTANEOUSLY IN MICE

THE study of autoimmune disease has hitherto been handicapped by the absence of any available condition in laboratory animals that was reasonably analogous to one of the human autoimmune diseases. Conditions such as Masugi nephritis in rats or experimental thrombocytopenic purpura in guineapigs, produced by antisera prepared in other species, have been studied extensively but are only partially relevant to the human problem. Nor has the lupus-erythematosus-like syndrome produced by hydrallazine in rabbits been productive. Bielchowsky, Helyer, and Howie [1] have, however, recently described an inbred strain of mice whose members spontaneously develop a high incidence of hæmolytic anæmia of an autoimmune type.

With their cooperation we have been able to establish a colony of their NZB/BL strain. The autoimmune nature of the disease has been confirmed by finding that the affected mice develop a positive "direct" Coombs test. Attempts have been made to transmit the disease from Coombs-positive to Coombs-negative mice by means of spleen cells.

MATERIALS AND METHODS

Inbred C_3H and C57B1 and outbred Hall Institute (HI) mice maintained in the laboratory were available for testing.

An anti-mouse-globulin serum prepared in rabbits from methanol-precipitated globulin, was absorbed with HI and C_3H red cells and used at dilutions of 1/5 and 1/50 in a "direct" Coombs test which was carried out on slides and read after 20 minutes at room temperature.

In the transmission experiments newborn (aged < 1 day) and young (aged 3-5 weeks) mice were inoculated intraperitoneally with a standard dose of 20×10^6 nucleated spleen cells suspended in buffered Earle's solution. Young recipients were Coombs-tested at least four times at weekly intervals after inoculation, and the newborns were tested either at 2 weeks or at 4 and 6 weeks after inoculation.

1. Bielchowsky, M., Helyer, B. J., Howie, J. B. *Proc. Univ. Otago med. Sch.* 1959, **37**, 9.

RESULTS

Repeated tests have shown that the Coombs test is always negative in NZB/BL mice less than 3 months old. Occasional positives are detected at 3 months and the incidence increases until almost 100% are Coombs-positive at 9 months. No positive Coombs tests have been found among old stock mice from the C_3H, C57B1, or HI strains.

Pooled spleen-cell suspensions from 4-week-old Coombs-negative NZB/BL mice, and individual spleen-cell suspensions from 10–12-month-old Coombs-positive donors, were inoculated into newborn and young NZB/BL, C_3H, and C57B1 mice. The results are shown in the table.

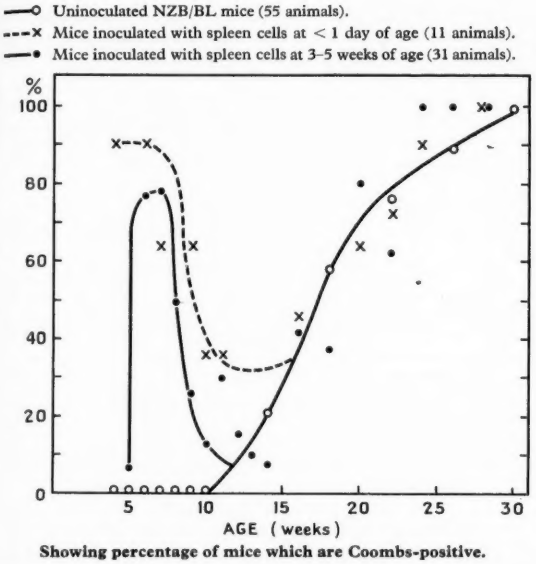
None of the mice receiving spleen cells from Coombs-negative donors became Coombs-positive within the test period, but when cells from Coombs-positive donors were inoculated into isologous mice some or all of the recipients in nine of the twelve experiments became Coombs-positive. In ten similar experiments the homologous C_3H and C57B1 recipients remained Coombs-negative. Infant C_3H mice inoculated with cells from the young unaffected donors died within 22 days of inoculation, with the symptoms of classical runt disease; infant C57/B1 and NZB/BL mice grew normally after receiving cells from positive or negative donors. One Coombs-positive donor was shown to have lymphoid leukæmia and the isologous recipients died with leukæmia but did not become Coombs-positive.

The Coombs test first became positive in the young recipients at the first, second, or occasionally the third weekly test after

ISOLOGOUS AND HOMOLOGOUS TRANSMISSION EXPERIMENTS WITH NZB/BL SPLEEN CELLS

Recipients		Proportion of recipients with positive Coombs tests	
Strain	Age	Coombs-negative donors	Coombs-positive donors
NZB/BL	< 1 day	0/4	10/11, 0/5*, 3/3
	3–5 weeks	0/11	3/3, 2/7, 0/3*, 5/5, 3/4, 0/5, 3/3, 3/4, 5/5
C_3H	3–5 weeks	0/4	0/5, 0/4, 0/4, 0/2
C57B1	< 1 day	0/12	0/8, 0/3
	3–5 weeks	0/5	0/4, 0/4, 0/3, 0/4

* Donor had leukæmia.



Showing percentage of mice which are Coombs-positive.

inoculation, and it remained positive for a variable time afterwards (see figure). Some inoculated recipients have remained positive until the uninoculated control mice in the experiment converted spontaneously, whereas others became negative after 4 or 5 weeks and later became positive again at about the normal age of conversion.

In four experiments a portion of the spleen-cell suspension from affected donors was frozen and thawed twice or three times or heated to 50° C. for 30 minutes. The recipients of the treated portions all remained Coombs-negative, whereas 16/16 of those receiving the untreated cells became Coombs-positive.

DISCUSSION

Our experience confirms that of Bielchowsky et al. (1959) that as mice of the NZB/BL strain age they develop a condition with all the characteristics of an acquired hæmolytic anæmia of autoimmune type. In the present work we have shown that the condition can be transferred to young isologous mice by inoculation of spleen cells from an older mouse with signs of the disease. Transfer of such cells was without effect in mice of two other strains nor could the Coombs-positive state be induced by transfer of spleen cells from young NZB/BL mice to isologous recipients.

Before the results are discussed, it is necessary to indicate the genetic status of the NZB/BL strain. There has been close inbreeding for at least 40 generations, and cross skin-grafting done with the assistance of Dr. J. Dineen has shown that all first grafts are accepted although hair growth and hair pigmentation in the grafts was often poor. On several occasions a second graft has been rejected, suggesting that the strain is not yet completely isogenic.

The delay in the appearance of the Coombs-positive state after cell transfer in 4-weeks-old mice and its persistence for several weeks in the mice injected in infancy precludes an explanation in terms of a simple passive transfer of antibody. Limitation of passage to the isologous strain eliminates any likelihood that an infective agent is involved. This is reinforced by the failure of frozen and thawed material to be effective. Everything is consistent with the straightforward interpretation that in the older animals there are altered cells in the spleen which can convey the disease to tolerant recipients. Either the cells can proliferate in the recipient and eventually give rise to the globulin that produces the Coombs reactivity of the red cells, or they provide conditions which will allow the recipient's own cells to take over this anomalous activity.

It is clear that the condition is closely similar to acquired hæmolytic anæmia of chronic type in human beings. Anæmia and other signs of blood destruction, direct Coombs-positive test, and enlarged spleen are all present. Interpretation will initially at least be subject to the same difficulties as have arisen in regard to the pathogenesis of the human disease.[2]

The first hypothesis to be considered is that the condition which we recognise by the Coombs-positive reaction is not of immunological origin but is due to the non-immunological liberation of a non-specific reactive globulin. This is probably not susceptible of disproof in the present stage of our experiments, but it is a rather sterile hypothesis. If it is true, we must think of the effective (abnormal) cells in the spleen as plasmacytes which have taken on the character of low-grade tumour cells. The analogy would then be with multiple myelomatosis; and the chief objection to such an interpretation is that neither in myelomatosis in man nor in any of the plasmacytomas of mice that have been described do we ever regularly observe a direct Coombs test or signs of hæmolytic anæmia.

We prefer the general hypothesis that this is an autoimmune condition in the sense that antibody is responsible for the Coombs-positive state and that in the transfer we are implanting immunologically competent cells analogous to the cells which will allow the transfer of capacity to produce classical antibody from an actively immunised donor to a tolerant recipient. The cells concerned in our mice, however, as in all autoimmune conditions, differ in being reactive against a normal constituent.

There are two approaches to a more specific interpretation of the phenomena by which such " forbidden clones " of cells develop with age and can be demonstrated by passage. Both assume that the cells are unresponsive to some normally effective homœostatic control. If we consider in the first instance only the spontaneous development of the condition, we can ascribe the failure of homœostasis either to (1) a general weakness of immunological homœostasis, allowing clones to flourish that would be eliminated in a normal animal, or (2) the emergence of clones of cells intrinsically more resistant to control. The fact that when mice are injected in infancy with established clones they may show the Coombs-positive state over long periods suggests that the cellular changes are primary.

In the further study of this condition our working hypothesis will be that the essential genetic lesion is an increased liability of immunologically competent cells to undergo somatic mutation toward resistance to immunological homœostasis. Only when the change involves a cell or clone which carries or can develop reactivity against accessible body components will there be any recognisable effect. This hypothesis calls for several experimental approaches that we hope to pursue.

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Reviews of Books

Samson Wright's Applied Physiology

10th ed. Revised by CYRIL A. KEELE, M.D., F.R.C.P., professor of pharmacology and therapeutics, University of London, at the Middlesex Hospital Medical School; ERIC NEIL, M.D., John Astor professor of physiology, University of London, at the Middlesex Hospital Medical School. London: Oxford University Press. 1961. Pp. 555. 60*s*.

IN the nine years since the last edition of Samson Wright there have been considerable changes in emphasis and factual knowledge in physiology, so a new edition is very welcome. At first sight the new volume is unrecognisable; the format and figure (growing stouter with the passing of years) of the old book have changed completely. It now has large double-column pages, mainly for economic reasons, as the new authors point out. In some ways the change in format is an improvement, but the book is now more difficult to balance and handle away from a table. This edition is almost entirely rewritten, and is the better for it. In the previous editions it was necessary to skip about, forwards and backwards, in order to cover a subject, and less of this is now necessary. It is all to the good that there is now a separate section devoted to the ear and eye; previously these were wedged between cutaneous senses and muscle tone. It is also an improvement that fœtal circulation is now treated under the heading of reproduction.

As might be expected of the authors, the discussion of pain is especially clear, and the sections on nervous regulation of the circulation and on muscle and peripheral nerve are authoritative. It is noteworthy that a large proportion of the matter in the last section refers to work done since the last edition. Amongst other new topics referred to or discussed are the development of the Schwann cell, the latest theories on renal activity, aldosterone, and Hashimoto disease, and the greater understanding of the differences in function of adrenaline and noradrenaline. The type and headings to subsections are clear, a number of old figures have been discarded without loss, and it is definitely on the credit side that some references are given at the end of each section. The index stood up to the tests to which it was subjected.

The authors, pharmacologist and physiologist, had a hard task in attempting to rejuvenate so famous a book. They have maintained the standard of the original author, and the book should continue to be a success.

Multiple-choice Examinations in Medicine

A guide for Examiner and examinee. J. P. HUBBARD, M.D., professor of public health, University of Pennsylvania; W. V. CLEMANS, director of testing services, National Board of Medical Examiners, Philadelphia. London: Henry Kimpton. 1961. Pp. 178. 28*s*.

THERE has long been a need for an authoritative account of American experience of objective examinations in medicine. It is well known in this country that they are widely used there, especially in the centralised examinations of the various national boards. A good deal is known by hearsay, and there have been a few papers, helpful though insufficiently detailed, but no systematic account. This book by two leading members of the National Board of Medical Examiners goes far to meet this need. The authors present the arguments in favour of their methods of examining with care and balance, and though they may from their position be regarded as having a vested interest in the methods, and it may be admitted that the conditions of the American National Board examinations are more favourable for their use than those of most medical examinations in this country, few unprejudiced readers could finish the book without believing that we have neglected these techniques. Especially valuable are the descriptions of the types of question possible, the pitfalls in the composition of papers, the methods of marking (including machine marking), and the methods of analysis. There is even a fascinating final-M.B.-level sample paper. The book is indispensable to anyone thinking of using objective papers, full of food for thought for any examiner in medicine and (incidentally) a useful insurance to anyone likely to be faced with any examination in medicine in the U.S.A.

Molecular Genetics and Human Disease

Editor: L. I. GARDNER, M.D., professor of pediatrics, State University of New York. Springfield, Ill.: C. C. Thomas. Oxford: Blackwell Scientific Publications. 1961. Pp. 297. 92*s*.

Human Chromosome Abnormalities

Editors: W. M. DAVIDSON and D. R. SMITH. London: Staples Press. 1961. Pp. 148. 21*s*.

THESE two symposia deal with aspects of human genetics; the first being chiefly biochemical with some sections on chromosomes, the second purely chromosomal. Both, as is often the way of reports on symposia, have been a long time printing, for both were held in 1959. The American symposium (to whose report some substantially more recent material seems to have been added) was obviously a lively one, with far-ranging discussions reported in detail. Papers by Crick on D.N.A., Kirkman on primaquine sensitivity, Russell on mouse genetics, and Polani on Klinefelter's syndrome seem to have been the highlights.

The British symposium, though already outdated by the pace of recent advances, might be allowed a place in the history of medicine. The first meeting to be devoted to the subject, it was held within seven months of the first publications on human chromosomal abnormalities, and presents an astonishing picture of the amount of work done in that short space of time. A great deal of the matter is still sound, and (except for one or two papers which have been rewritten at excessive length after the symposium was over) it communicates even now something of the excitement of the opening up of a new field. A good deal of it is much easier to follow than later more esoteric publications. Both symposia are very well edited and well produced.

Problems of Infection, Immunity and Allergy in Acute Radiation Diseases

N. N. KLEMKARSKAYA, O. G. ALEXSEYEVA, R. V. PETROV, V. F. SOSOVA. Oxford: Pergamon Press. 1961. Pp. 165. 50*s*. Translated by Lydia Venters from the original volume published in Moscow by Medgiz, 1958.

ENGLISH translations of Russian books on radiobiology are sufficiently rare to warrant special attention. The publishers' notice at the front of this book suggests a review of recent work, but over 97% of the 326 references are to work published in 1956 or before. The five chapters deal with the following aspects of acute radiation disease: "autoinfection" by the animal's normal microbial flora, natural immunity, acquired immunity, allergy, and infectious diseases. Though the references are not recent, these fields are reviewed adequately with a reasonable balance between Russian and non-Russian work.

In the first chapter it is claimed that bacteria resident in an irradiated animal change their characteristics and become less sensitive to antibiotics. The evidence for this interesting claim is meagre and in itself unconvincing. In some of the examples given the specific type of bacterium being investigated is not stated. In chapter 5 the authors state their belief in the "great significance" of "auto-allergy" in relation to acute radiation sickness. This is not a new idea. Although much is said about the role of allergy in acute radiation sickness, a few experiments demonstrating the quantitative protective effect of antiallergic drugs would be much more to the point. Some strange expressions clearly derive from imperfect translation. "Blue pus bacillus" seems to refer to *Pseudomonas pyocyanea*, but what are "blue-green rods"? The non-letterpress setting and photolithography make the text unattractive, but the alternative would have been to raise the price still higher.

The book's interest lies in the fact that it is one of the few places where a review of Russian radiobiological literature is available in English. It suffers seriously from being out of date, but the research-worker specially concerned in these problems will find this volume of interest.

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Primary Hyperparathyroidism

IN the past ten years, with increasing awareness, hyperparathyroidism has been diagnosed more and more commonly. This trend is well illustrated by reports from Detroit [1] and from Belfast, where the observed incidence is now about 10 cases per 1,000,000 per annum.[2] But, despite this increased awareness, the diagnosis is often reached by serendipity [3]; in each of a series of 21 cases, reported only last year, the diagnosis became clear accidentally during operations on the neck.[4] Yet this disorder, if sought, is not difficult to detect [5]; and its recognition is important since, untreated, it is potentially fatal, whereas treatment can succeed if the diagnosis is made before progressive renal disease has developed.

Hyperparathyroid bone disease was the first form of the disorder to be recognised. The radiological changes are characteristic; the biochemical changes of raised serum-calcium and lowered serum-phosphorus are usually present continuously and to a notable degree, and in addition the serum-alkaline-phosphatase is raised in proportion to the amount of bone change. But, though most of the published series of cases of hyperparathyroidism in the 1930s and 1940s were largely composed of bone cases, this is by no means the commonest form of the disease. When ALBRIGHT reviewed the earlier cases he was struck by the fact that many of these patients had renal stones, and he began to screen patients with renal stones in the hope of finding further cases of hyperparathyroidism. This policy quickly yielded results,[6] but the true prevalence of hyperparathyroidism among patients with renal stones remains unknown. As early as 1942 COPE [7] suggested that it was between 10 and 15%. FETTER and MCCUSKEY,[8] however, last year reported only 6 cases among 172 patients who had undergone operation on account of renal stones. They pointed to the difficulties of diagnosing this form of hyperparathyroidism—notably the tendency for these patients to have a normal serum-calcium at times, which led to delay in diagnosis in 3 of their cases. Others, too, have encountered this difficulty; and MCGEOWN and MORRISON [2] suggest that the serum-calcium should be estimated at least four times over a period of months in all patients with calcareous renal stones. Of their series of 405 patients with renal stones, over 17% were found to have hyperparathyroidism.[9] Hyperparathyroidism would be expected to be commoner among patients who have had recurrent calculi; but if the calculi are composed of calcium salts the diagnosis should be considered without waiting for these to recur.

Many patients with hyperparathyroidism have symptoms suggesting peptic ulceration; and in some the disease manifests itself by a long history of peptic ulcer, without bone disease or renal stones. This form closely resembles the milk-alkali syndrome, from which it may be very difficult to distinguish, especially as in both disorders renal function is often much impaired. But distinction of the two conditions is essential, because their treatment is quite different. In hyperparathyroidism, even at a late stage, parathyroidectomy may improve wellbeing and prolong life. FRAME and HAUBRICH [10] have screened 300 patients with peptic ulcers by estimating the serum-calcium, repeating the estimation if the level was above the normal range. In 4 patients parathyroid adenomas were found by this means; and 5 additional patients had an initially raised serum-calcium although later tests did not suggest hyperparathyroidism. In view of the tendency of the serum-calcium to fluctuate in hyperparathyroidism, a single estimation is not sufficient to exclude this condition; and repeated estimation in all cases might have uncovered further instances of hyperparathyroidism. Peptic ulcer is very much commoner than hyperparathyroidism, and it would be difficult to screen all patients with peptic ulcer adequately. In patients with both peptic ulcer and renal calculi the indication for investigation of parathyroid function is stronger (although it should not be forgotten that in hyperparathyroidism the patient may have both peptic ulcer and severely impaired renal function without renal calculi). Peptic ulcer is so common that it would be expected to coexist fortuitously in some cases of hyperparathyroidism,[11] and in such cases the ulcer would persist after the hyperparathyroidism is terminated; but in most cases of hyperparathyroidism ulcer symptoms are relieved by parathyroidectomy.[12] Loss of appetite and persistent nausea and vomiting are common in this disease, and the loss of muscular tone associated with the hypercalcæmia leads to obstinate constipation; but these non-specific features are unlikely to arouse suspicion of the true diagnosis.

While most cases of hyperparathyroidism fall into one of the groups already mentioned, it may manifest itself in many other guises. Polyuria and polydipsia may be prominent and suggest diabetes insipidus. Muscular weakness may overshadow other symptoms.[13] Mental changes may develop in hyperparathyroidism,[14] as in other types of hypercalcæmia, and vary from irritability, impairment of memory, and mild confusion to delusional psychosis. (Perhaps some undiagnosed cases of hyperparathyroidism are to be found in mental hospitals.)

1. Micher, W. C., Thibaudeau, T., Frame, B. *Arch. intern. Med.* 1961, **107**, 361.
2. McGeown, M. G., Morrison E. *Postgrad. med. J.* 1959, **35**, 330.
3. Randall, R. V., Keating, F. R., Jr. *Trans. Ass. Amer. Phycns*, 1958, **71**, 77.
4. Ramsdall, J. A., Black, B. M., Woolner, L. B., Keating, F. R., Jr. *Surg. Gynec. Obstet.* 1960, **111**, 451.
5. Black, B. M. *Amer. J. Surg.* 1958, **96**, 613.
6. Albright, F., Baird, P. C., Cope, O., Bloomberg, E. *Amer. J. med. Sci.* 1934, **49**, 187.
7. Cope, O. *J. Miss. med. Ass.* 1942, **39**, 273.
8. Fetter, T. R., McCuskey, B. M. *J. Urol.* 1960, **84**, 213.
9. McGeown, M. G. *Lancet*, 1961, i, 586.
10. Frame, B., Haubrich, W. S. *Arch. intern. Med.* 1960, **105**, 536.
11. Spiro, H. M. *Gastroenterology*, 1960, **39**, 544.
12. Adesola, A. O., Ward, J. T., McGeown, M. G., Welbourn, R. B. *Brit. J. Surg.* 1961, **48**, 112.
13. Murphy, T. R., ReMine, W. G., Burbank, M. K. *Proc. Mayo Clin.* 1960, **35**, 629.
14. Snapper, I. Bone Diseases in Medical Practice. New York, 1957.

COPE et al.[15] found that occasionally pancreatitis provided a clue to hyperparathyroidism. Rarely tetany in the newborn has led to the discovery of hyperparathyroidism in the mother.[16–19] Hyperparathyroidism may manifest itself as a hypercalcæmic crisis.[20] The patient becomes severely ill with abdominal pain, vomiting, oliguria, and confusion, with progression to coma and death unless the condition is recognised. A previous history of renal stones or bone pain may enable the condition to be diagnosed during life, but most cases are recognised only at necropsy.

The diagnosis of hyperparathyroidism almost always depends on the discovery of a raised serum-calcium level. The change may be slight, and is often present only intermittently—hence the need for repeated estimations. A few cases have been diagnosed in the absence of a raised serum-calcium; in such cases the necessary clue has usually been severely impaired renal function. A lowered serum-phosphorus is an even less constant sign, for the level is no longer low when renal function becomes moderately impaired, and may be normal even with good renal function. Tests based on the renal excretion of phosphorus are often unhelpful, and are particularly liable to mislead in patients with renal stones.[2 21–23] Urinary excretion of calcium is usually increased unless renal function is impaired, but many patients with renal stones have hypercalciura without having hyperparathyroidism. The changes after intravenous infusion of calcium were at first thought to distinguish hyperparathyroidism from the euparathyroid state[24]; but in hyperparathyroidism these changes are often lacking, and similar changes may be found with other types of hypercalcæmia[25] and renal stones.[26] FOURMAN et al.[27] investigated the renal handling of water and hydrogen ion; unfortunately, while some hyperparathyroid subjects have abnormalities, these are by no means the rule, and similar changes occur without hyperparathyroidism.[26] LLOYD and ROSE[28] have reported that the ionised fraction of the serum-calcium is raised in hyperparathyroidism, even when the total serum-calcium is normal. This test is technically difficult and has not been widely used; but HYDE et al.[29] found the ionised fraction normal at times when the total serum-calcium was normal, and it is raised in other types of hypercalcæmia.[30] GORDAN[31] reported a rise in the α_2 and β fractions of the serum-proteins in hyperparathyroidism, but MCGEOWN[26] has not confirmed this. The α_2 fraction is raised in infantile hypercalcæmia,[32] and any increase in this fraction is more likely to be related to the hypercalcæmia itself than to hyperparathyroidism.

Once the serum-calcium is found to be raised, other causes of hypercalcæmia must be excluded. Electrophoresis of the serum-proteins, though not diagnostic of hyperparathyroidism, should be undertaken to exclude multiple myelomatosis and sarcoidosis. Vitamin-D intoxication may be suggested by the history, and, if there is any reason to suspect this, a short course of cortisone should be given; this will abolish the hypercalcæmia of vitamin-D overdosage and of sarcoidosis but will not affect the hypercalcæmia of hyperparathyroidism.[33] Secondary carcinomatosis affecting bone is fairly easily excluded; but a hypernephroma can produce hypercalcæmia without obvious metastasis in the bones. The milk-alkali syndrome can be particularly difficult to distinguish from hyperparathyroidism because in the latter condition peptic ulceration may dominate the picture. Acute osteoporosis from disuse has led to confusion with hyperparathyroidism.[34]

It may well be asked whether all the effort required to detect hyperparathyroidism, especially the milder cases, is worth while; for, while it is potentially fatal, it usually has a very protracted course, sometimes lasting thirty years. On the other hand the untreated patient suffers ill health from bone pains leading to fractures and crippling deformities, or from recurrent renal stones with resultant damage to the kidneys, and may have an intractable peptic ulcer. If the condition is diagnosed and the hyperactive parathyroid tissue is found and removed, bones heal, the tendency for renal calculi to form is greatly reduced,[9] and the symptoms of peptic ulceration are usually relieved.[12] These benefits amply justify the effort involved in diagnosis.

Diagnosis of Disc Lesions

To recognise the causes of lumbago and sciatica is important, and any new technique that may help in more exact diagnosis must be welcome. A lecture[35] given in South Africa by HARMON, of San Francisco, discusses the value of two tests—namely, radiography of the lumbar spine during flexion and extension, and injection of saline solution into the nucleus pulposus.[36]

If one excludes the relatively small number of patients with gross pathological conditions such as tumours, ankylosing spondylitis, tuberculosis, and spondylolisthesis, the biggest single cause of lumbago and sciatica is loss of elasticity of the nucleus pulposus. It is well known that in childhood the nucleus pulposus is large and fluid and that with increasing age it gradually becomes smaller, dehydrated, and ultimately fibrotic.[36] This process is normally accompanied by a diminution in the elasticity of the disc. An injury such as a crush fracture of a vertebral body may precipitate acute degeneration of the nucleus pulposus, predisposing, so

15. Cope, O., Culver, P. J., Mixter, C. J., Jr., Nardi, G. L. *Ann. Surg.* 1957, **145**, 857.
16. Friderichsen, C. *Lancet*, 1939, i, 85.
17. Bruce, J., Strong, J. A. *Quart. J. Med.* 1955, **24**, 307.
18. Walton, R. L. *Pediatrics*, 1954, **13**, 227.
19. McGeown, M. G., Field, C. M. B. *Lancet*, 1960, ii, 1268.
20. Thomas, W. C., Wiswell, J. G., Connor, T. B., Howard J. E. *Amer. J. Med.* 1958, **24**, 229.
21. Reynolds, T. B., Lanman, H., Tupikova, N. *J. clin. Endocrin.* 1960, **20**, 1136.
22. Morgan, H. G., Stewart, W. K., Grieve, J. *J. clin. Path.* 1960, **13**, 494.
23. Hodgkinson, A. *Clin. Sci.* 1961, **21**, 125.
24. Howard, J. E., Hopkins, T. R., Connor, T. B. *J. clin. Endocrin.* 1953, **13**, 1.
25. Thomas, W. C., Connor, T. B., Morgan, H. G. *J. Lab. clin. Med.* 1958, **52**, 11.
26. McGeown, M. G. *Proc. Ass. clin. Biochem.* 1961, **1**, 46.
27. Fourman, P., McConkey, B., Smith, J. W. G. *Lancet*, 1960, i, 619.
28. Lloyd, H. M., Rose, G. A. *ibid.* 1958, ii, 1258.
29. Hyde, R. D., Jones, R. V., McSwiney, R. R., Prunty, F. T. G. *ibid.* 1960, i, 250.
30. Fowler, D. I., Fone, D. J., Cooke, W. T. *ibid.* Aug. 5, 1961, p. 284.
31. Gordan, G. S. *Acta Endocr., Copenhagen*, 1960, **35**, suppl. 51, p. 463.
32. Creery, R. D. G., Neill, D. W. *Lancet*, 1954, ii, 110.
33. Dent, C. E. *Brit. med. J.* 1956, i, 230.
34. Albright, F., Reifenstein, E.C. The Parathyroid Glands and Metabolic Bone Disease; p. 85. Baltimore, 1948.
35. Harmon, P. H. *Trans. Coll. Phycns Surg. Gynæc. S. Afr.* May, 1961 p. 29.
36. Bick, E. N. *J. Mt Sinai Hosp.* 1952, **19**, 490.

to speak, to premature ageing of the disc. If degeneration proceeds smoothly, restriction of spinal movement will be gradual and painless; but during this time the spine is especially vulnerable to injury. The loss of disc turgor throws an increased strain on the capsules of the posterior articulations and spinal ligaments but does not cause pressure on the cauda equina or nerve-roots.

In deciding on treatment it is important to distinguish between tears and protrusions of the annulus, which usually require surgical removal, and degeneration of the nucleus pulposus, which usually becomes painless spontaneously—i.e. there is clinical recovery with conservative treatment. In many patients who present with the classical signs of sciatica the diagnosis is easy, but in about 20% of those with recurrent incapacitating sciatica or lumbago the clinical signs are atypical. Four main auxilliary methods of investigation have been employed:

Myelography with an oil-soluble medium will reveal intradural tumours and large disc protrusions, and indicate the level, but it will not demonstrate small lateral protrusions at the lumbosacral level.

Myelography with a water-soluble medium has been extensively used in Sweden [37] and Denmark. It has the disadvantage that a spinal anæsthetic must be used; and the agent employed ('Abrodil') is not obtainable on the English market. Very beautiful pictures of the nerve-roots can be produced, and lateral protrusions at the lumbosacral level can be demonstrated; but the method requires considerable care, skill, and experience, and at present it is unlikely to be used widely in this country.

Nucleography has also been used notably by ERLACHER [38] and HIRSCH.[39] Where there is a large annular tear it yields positive evidence; but interpretation may be difficult where the tear is slight. Nucleography has never been widely adopted here; and even in certain clinics in Sweden it is used less often than it was.

Electromyography will give positive evidence of involvement of motor neurones; but it takes time. As with all sampling procedures, there are certain possibilities of error, and its localising value is uncertain.[40]

HARMON points out that radiographs of the lumbar spine taken in flexion and extension will reveal instability and/or limitation of movement. This is a useful screening test which, however, gives a number of "false positives"—i.e., there may be limitation of movement with symptomless degenerative lesions. Of 259 disc excisions only 2% showed no abnormality on flexion-extension radiographs. Out of 62 control patients who had no symptoms, 15% had limitation of flexion-extension, and out of 363 patients who had previously had painful discs but were now symptom-free, 36% had limited movement. Most of us have one or more degenerate discs, but not all of us have lumbago and sciatica—at least, not all the time. At operation HARMON employs a further test—namely, the direct injection of saline into the nucleus pulposus. In his experience, if it is possible to inject more than 1·5 ml. the disc is abnormal. Using this technique he finds that in 43% of the patients more than one disc is affected; and isolated degeneration of the L4–5 disc was found in only 16%.

37. Knutsson, B. *Acta orthopæd. scand.* 1961, suppl. no. 59.
38. Erlacher, P. R. *J. Bone Jt Surg.* 1952, **34B**, 204.
39. Hirsch, C. *Acta orthopæd. scand.* 1949, **18**, 132.
40. Shea, P. A., Woods, W. W., Werden, D. H., *Arch. Neurol. Psychiat.* 1950, **64**, 93.

It is difficult to correlate HARMON'S findings in California with experience in this country, where the operation-rate is lower and where we are more apt to advise the patient to tolerate a certain amount of pain, at any rate for a time, in the belief that many degenerating discs cure themselves. Nevertheless it is clear that there are difficult borderline cases where these auxiliary tests are of great value. Any surgeon would be very pleased if he could obtain results as good as HARMON'S—namely, 87% excellent and 9% good.

Annotations

EMERGENCY RESUSCITATION

THE symposium on Emergency Resuscitation held last month in Norway, of which an account is given on p. 654, is of interest not so much for any new information coming out of it as for a crystallisation of ideas.

The superiority of the expired-air method to manual methods of artificial respiration is now too firmly established to require comment: consideration has shifted to methods of teaching the expired-air method not only to recognised first-aid workers but to the public at large. It can easily be taught; but its teaching, outside the family circle, requires aids. These may be two-dimensional, in the form of films, pictures, and diagrams, or three-dimensional, in the form of mannikins and models. Comparison suggests that the latter are preferable, at any rate for teaching children; and in the symposium it was suggested that it is in the schoolroom, and on a nationwide basis, that the method should primarily be taught. The Scandinavian countries have taken the lead in this, and in Norway instruction is now compulsory for all State school-children as they come into the 12–14 age-group. This involves the instruction of about 130,000 children a year. Hundreds of schoolteachers have already been instructed in the method, and shown how to teach their pupils. A lifelike mannikin, which is effective and relatively cheap, is manufactured in Norway, and 580 of these have been distributed among the schools. Two periods of 45 minutes have been found sufficient to instruct a class of 30 children. The way in which the Norwegians have grasped the nettle should inspire other countries, and we hope that public-health and educational authorities in this country as well as the first-aid and Civil Defence organisations will profit by it. They have been dragging their feet for too long; though acknowledging that the expired-air method is the best, they have been unwilling to face the problems of teaching it, or the mental reorientation and the rewriting of training manuals which its adoption must entail.

Some sympathy must be felt with responsible lay teachers of first-aid. They have been required to adapt themselves several times to what some of them regard, with understandable scepticism, as changes in medical fashion. Now they are being asked to make an even more radical and difficult departure from established methods. Nor can the medical scientists give them the assurance they seek—that this time the method has come to stay, that there can be nothing better. All they can be told is that it looks like the best at the moment, and that the means by which the possible methods can be judged and compared are now much more reliable than they were.

The idea that the teaching of this form of resuscitation

should be begun in the schools and should be included as a matter of course in the curriculum captures the imagination. The provision of training aids on an adequate scale in this country would be expensive. The Norwegian mannikin costs about £35. The Norwegians have one to every 200 children taught; but for Britain, with its denser population and good communications, one might be made to suffice for many times this figure. Lord Nuffield's well-directed generosity in providing this country with cabinet respirators is still fresh in many memories. Perhaps some other benefactor or charitable trust might help to defray the cost of an enterprise that would result in an even greater saving of life.

INNOCENT MURMURS IN CHILDREN

CARDIAC murmurs can be heard in healthy children, sometimes giving rise to diagnostic problems. It is important that their innocent nature be both recognised and clearly stated, so that no suspicion shall remain in the mind of the child or parents that the heart is in some way abnormal. Intensity alone is not always a good guide to the significance of a murmur, and Castle [1] has described the clinical identification of five common innocent murmurs by more reliable means.

A vibratory murmur, which may be musical or groaning, occurs in midsystole and is usually best heard along or somewhat lateral to the left sternal edge. Its origin is still undecided. Its short duration distinguishes it from the murmurs of ventricular septal defect and mitral regurgitation, which are pansystolic, continuing right up to the second heart sound. The pulmonary ejection murmur, whose origin is self-explanatory, is also midsystolic but is blowing in quality. It is usually best heard in the pulmonary area, although it may be well transmitted to the apex. It is accentuated by anything which increases the pulmonary blood-flow, including exercise and fever. Lewis et al.[2] have shown by intracardiac phonocardiography that a similar murmur can be recorded in the main pulmonary artery of all healthy subjects. Its intensity and the thickness of the chest wall presumably determine whether it is audible externally. Atrial septal defects and mild pulmonary stenosis both give rise to pulmonary ejection murmurs which may be indistinguishable from the innocent form. These conditions must be excluded by the absence of their other physical signs, important among which are changes in the second heart sound. In healthy children this sound is clearly split into its aortic and pulmonary components on inspiration, whereas on expiration splitting is slight or absent.[3–6] When atrial septal defect is present the splitting is rather wide and does not vary appreciably with respiration.[6 7] In pulmonary stenosis respiratory variation persists; but there is abnormally wide splitting best detected in expiration, and an ejection sound can also usually be heard when the condition is mild.[8] The venous hum is a continuous murmur best heard at the root of the neck on the right side. It must be distinguished from the murmur of a patent ductus arteriosus. This is easy since the hum disappears or becomes much softer if the veins on the right side of the neck are compressed or the patient lies flat. Cardiorespiratory murmurs and systolic clicks are less common, tend to be bizarre in their characteristics and timing, and are unlikely to be confused with organic murmurs. Arterial murmurs, arising in the large vessels, are sometimes heard in the root of the neck. They should not be difficult to distinguish from the murmur of aortic stenosis, since they are always much louder in the neck than at the aortic area, where often they cannot be heard at all.

Thus the innocence of a cardiac murmur can almost always be established, without recourse to special investigations, by careful attention to its site and timing combined with analysis of the second heart sound. This is due largely to the increased knowledge of heart sounds and murmurs, particularly of their timing, obtained by phonocardiography.

1. Castle, R. F. *J. Amer. med. Ass.* 1961, **177**, 1.
2. Lewis, D. H., Ertugrul, A., Deitz, G. W., Wallace, J. D., Brown, J. R., Jr., Moghadam, A. *Pediatrics*, 1959, **23**, 837.
3. Leatham, A., Towers, M. *Brit. Heart J.* 1951, **13**, 575.
4. Leatham, A. *Lancet*, 1954, ii, 607.
5. Boyer, S. H., Chisholm, A. W. *Circulation*, 1958, **18**, 1010.
6. Shafter, H. A. *Amer. J. Cardiol.* 1960, **6**, 1013.
7. Leatham, A., Gray, I. *Brit. Heart J.* 1956, **18**, 193.
8. Leatham, A., Weitzman, D. *ibid.* 1957, **19**, 303.

BIOLOGICAL STANDARDISATION

How many doctors, when they are about to inject a vaccine, an antiserum, or an antibiotic, ever hesitate and wonder whether the material is both safe and potent? Why should they, when the label on the container either states or implies that it is sterile, and the dose or strength is similarly declared? But to ensure that the label's message can be accepted with this confidence, the manufacturer has had to discharge a very heavy responsibility. Even with pure chemicals the task of ensuring that they are free from noxious ingredients is a continuous and onerous one. With " biologicals ", the efforts to establish and maintain standards is far more difficult and costly. What is more, it calls for international understanding and agreement if these products are to be sold satisfactorily between one country and another.

To this end, in London, on Aug. 28–Sept. 1, the permanent section on biological standardisation of the International Association of Microbiological Societies held its seventh annual congress, with Lord Cohen of Birkenhead as president and Prof. A. A. Miles as chairman. To the success of the meeting Dr. J. Ungar, as chairman of the organising committee, and Mr. E. C. Hulse, as secretary, also contributed a large share. Nearly 300 delegates were registered and 32 countries were represented, including Poland, Hungary, Yugoslavia, and the U.S.S.R. The scientific part of the programme covered such topics as international standards, adventitious agents in vaccines, sterility testing, diagnostic sera for virus infections, tuberculin, staphylococcal antigens, B.C.G. vaccine, and antiviral agents.

What became at once apparent was the vast amount of research now being undertaken in these various subjects and the complexity of the problems arising. Indeed, a general practitioner might well have been dismayed by the obvious differences of opinion and the occasionally fierce arguments, and he might have wondered whether he could really put his trust in anything at all. Concerning poliomyelitis vaccine, for example, what is the true significance of the so-called " vacuolating agents "? The feeling is that they should not be there, and the experts are on their guard against them. But are they in fact of sinister import? And when it comes to diagnosing virus infections serologically, how far do the laboratory tests truly help the clinician or advance treatment? In sterility control and testing, the extreme measures which the manufacturers and control authorities entertain might flabbergast the

doctor who thinks solely of absolute sterility on the one hand and dangerous contamination on the other. His own simple manœuvres of boiling, immersing, and flaming seem primitive by comparison. Then, with tuberculin, vast campaigns for the eradication of tuberculosis have been based on skin reactions, often assessed quantitatively. Yet the standardisation of the agent employed—that is to say, tuberculin—is beset with mysterious variables. Moreover, as new vaccines arise one after another, the clinician will adopt them only when he is certain that they will accomplish their intentions without any complications for the patient. It is easily overlooked that the development of a vaccine to this stage involves meticulous laboratory studies, international cooperation on standards, and careful and extensive checking in the field. Lastly, it is perhaps not always realised by the medical profession how favourably served they are by contrast to their colleagues in animal practice. It was arresting to learn that upwards of 50% of veterinary prophylactics examined were deficient in potency.

The crucial part played by the World Health Organisation is one of the most valuable activities of that institution. Through the National Institute for Medical Research, at Mill Hill in London, and the State Serum Institute in Copenhagen, it provides for the establishment and supply of some hundreds of international standards that are used, adhered to, and respected throughout the world. In seeing that the separate laboratories and manufacturers in the various countries issue products which conform with the accepted preparations, the national control authorities are concerned. In the United Kingdom the Ministry of Health exercises this supervision under the Therapeutic Substances Act which, with modification, has been in operation since 1925. In the end, though, it is the manufacturers themselves who must not only see that the existing standards are observed but also pursue their researches to see if they can be bettered. In biological substances, the industry has a very big stake, both financially and in technical personnel. That is why it is imperative that their staff should have the opportunity to meet men and women from Government laboratories, research institutes, and university departments to discuss their difficulties and set course for the future. In this way the recent congress occupies a unique place. Doctors and other scientists from all sides, but with one aim in common—the furtherance and more effective use of biological products in medicine and in animal health—were able to exchange ideas regardless of their parochial affiliations. No epoch-making discoveries were announced; few of the participants were entirely converted from one line of thought to another; but all went away having their views and beliefs refreshed and adjusted in a way that would otherwise have been impossible.

PLASMIN IN OCCLUSION OF THE CENTRAL RETINAL VESSELS

SPECIFIC therapy for intravascular clotting became feasible with the advent of heparin. In thrombosis of the central retinal vein, its effects could be assessed fairly readily, because the lesion could be observed ophthalmoscopically and any response easily checked by testing visual acuity. But anticoagulant therapy, though still widely used, has on the whole proved disappointing in retinal thrombosis, for the trouble arises more often from degenerative changes in the vein than from anomalies of blood-clotting. The introduction of purified proteolytic and fibrinolytic enzymes made possible a more direct attack on the clot, and experimental studies have shown the feasibility of actually digesting the clot. Experimentally the best results have come from injecting plasmin directly into the thrombus, which could be either dissolved or made sufficiently mobile to be "milked" into a position accessible to direct removal.

Some four years ago Cliffton [1] reported on the use of plasmin in 40 patients. It was clear that the side-effects were substantial but that the method was not unpromising, though in each of 2 cases of thrombosis of the central retinal vein no substantial improvement resulted from this treatment. Subsequent reports on the use of plasmin in thrombosis of the central retinal veins have been few and inconclusive; but Howden [2] reported a gratifying response in a patient with thrombosis of two days' standing, and now Hecker and Zweng [3] have recorded improvement in a man with occlusion of the central retinal artery—recovery occurring after other methods had been tried unsuccessfully for three days. In contrast, they report in an addendum that in 2 further such cases, treated within twenty-four and seventy-two hours of the onset of symptoms, no benefit ensued; but they record another successful outcome in a patient in whom both inferior branches of the central retinal artery were partly occluded.

Occlusion of the central retinal artery has probably an even more complex pathology than thrombosis of the central vein. Arterial occlusion is sometimes due entirely to spasm, without any thrombotic changes. There are therefore considerable difficulties in any critical assessment of a new remedy. Nevertheless such an assessment should be attempted with plasmin.

POLYCYTHÆMIA IN EMPHYSEMA

"POLYCYTHÆMIA" means a state in which there is an excess of blood-cells in the organism; but the definition is customarily restricted to denote an excess of red cells per unit volume of blood. Thus defined, polycythæmia is associated with most conditions in which the arterial blood is not fully saturated with oxygen. For example, the red-cell counts of residents in high mountains are substantially raised, and the rises have been shown to be related to the degree of unsaturation of the arterial blood. Similarly in patients with cyanotic congenital heart-disease very high counts are usual. This change is generally ascribed to increased production of red cells by the marrow in response to oxygen lack in its blood-supply. The increased red-cell count enhances the oxygen-carrying capacity of the blood and curtails the fall in partial pressure of oxygen in the blood as it passes through the capillaries; and, since the partial pressure of oxygen in the venous blood determines the degree of oxygen lack in tissues, this increase tends to compensate for the lowered partial pressure of oxygen in the arterial blood.

Even in those patients with emphysema in whom the partial pressure of oxygen in the arterial blood is lower than normal, an increase in the red-cell count is rare. Several explanations of this apparent exception to the rule have been put forward. The likeliest has seemed to be that the chronic infection associated with emphysema inhibits the hæmopoietic stimulus—namely, oxygen deficiency—

1. Cliffton, E. E. *Ann. N.Y. Acad. Sci.* 1957, **68**, 209.
2. Howden, G. D. *Canad. med. Ass. J.* 1959, **81**, 382.
3. Hecker, S. P., Zweng, H. C. *J. Amer. med. Ass.* 1961, **176**, 1067.

though infection is not constantly associated with emphysema. Shaw and Simpson [1] have now elucidated this problem. They began their study by considering only patients in whom arterial oxygen saturation was persistently low over a period of at least a year, since it seemed possible that intermittent lack of oxygen might not stimulate red-cell formation.[2] These workers used radioactive iron to study erythropoiesis, and radioactive chromium to measure plasma-volume. They found that the pattern of iron-binding capacity and the increases in the plasma-iron after their patients had been given an oral dose were typical of iron deficiency but quite unlike those reported in the anæmia of infection. At the same time they found that the patients' plasma-volume was nearly 50% higher than in the controls, the greatest values being in those with a past history of heart-failure. There was no evidence of increased red-cell destruction, and the patients did have a substantial increase in red cells expressed as a fraction of body-weight but not expressed as a fraction of blood-volume. In other words the patients had a true plethora of red cells but were not polycythæmic according to the customary restricted definition. Quantitative studies showed that the red-cell volume (in ml. per kg. body-weight) bore the same linear relationship to the percentage saturation of the arterial blood both in the group of patients and in dwellers at high altitudes.

In answering the question Why does the red-cell count not rise in hypoxic emphysema? Shaw and Simpson have posed another: Why does the plasma-volume rise at the same rate as the red-cell volume? Clearly the answer lies in the interrelation between pulmonary and hæmodynamic function and not, as has hitherto been thought, in that between pulmonary and hæmopoietic function.

ROBINSON'S TRAVELS

WORLD Mental Health year, which ends this month with the congress of the World Federation for Mental Health in Paris, was chosen by the National Association for Mental Health as the appropriate time for a selective global review of other countries' mental-health services. With the help of the Bruern Foundation, they offered Mr. Kenneth Robinson, M.P., a travelling fellowship which has enabled him to visit Holland, France, the United States, and the Soviet Union. In his report [3] on his comparative study tour he admits that he was somewhat surprised everywhere to meet so many familiar anxieties, difficulties, and pressures. He was heartened to find that everyone was moving in the same therapeutic direction—"towards community care, towards more dynamic treatment, towards a more liberal hospital atmosphere, and towards public enlightenment about the nature of mental disorder". But progress is uneven, though in each country he visited he was impressed by promising spearheads.

Mr. Robinson is clearly a fair-minded assessor and it is reassuring that he thinks that on the broad front no country has proceeded so far as Britain. At some points, indeed, he holds that we have a lead—notably in the introduction of the open-door policy, in the reablement of the long-stay patient, and in the use of non-medical therapy, such as factory projects. Many other countries are handicapped by outmoded legislation, and the provisions of our new Mental Health Act are the envy of foreign psychiatrists. Most important of all, he considers, is the fact that the actual care and treatment offered to patients in our progressive hospitals are unequalled. Nowhere did he find a more "liberal, permissive, therapeutic atmosphere". One reason for this, he suggests, is that our hospitals are more generously staffed with trained nurses. The shortage of trained nurses everywhere, except in the Soviet Union, is apparently acute, and by the end of his tour he was startled to find that he had begun to think that Britain was "relatively fortunate".

But there are points where we lag behind other countries. In the United States and in France Mr. Robinson saw new mental hospital buildings which were incomparably better than anything we have yet to show. For instance, Dr. Sivadon, one of the authors of the W.H.O. report on the design of psychiatric hospitals,[4] is building a 300-bed hospital at Château de la Vallière, at a cost of £7000 a bed, which will provide a flexible therapeutic background of comparative isolation, a small group, a larger group, or contact with the community, according to the patient's needs.

Mr. Robinson has often urged, at Westminster and elsewhere, that psychiatry should be given a larger place in the medical curriculum, and this opinion has been reinforced by what he saw. He comments on the "remarkable break-through" made by psychiatrists in the United States during the last five years. The teaching of psychological medicine there now receives much more emphasis, and in the University of California, for instance, it has been increased to over 10% of the students' study hours. A compulsory paper in psychological medicine is to be introduced into the National Board's final examination.

Only in the United States did Mr. Robinson find that enough money and people were being allocated to research. The National Institute of Mental Health at Bethesda has a budget of 101 million dollars of which 39 million goes to research, while 75 beds are set aside for mental health at the 500-bed clinical research centre at Bethesda. The institute also sponsors research projects in other parts of the States. One that interested Mr. Robinson was the clinical neuropharmacology centre in Saint Elizabeth's Hospital, Washington, run by Dr. Joel Elkes, who formerly held the chair of experimental psychiatry at Birmingham. At the centre, which has 350 beds, new research techniques applicable to a mental-hospital population are being studied.

Ultimately, progress in the care of the mentally ill depends on public opinion, and Mr. Robinson admits that this is hard to assess. In his view, though public interest is most intense in the United States it may have "some element of morbidity". But acceptance is important as well as awareness, and he was impressed by the tolerance and sympathy shown to these patients in the Soviet Union, though he fancied that there seemed to be a tendency to regard subnormality (as opposed to mental illness) as a slur on their form of society. In this country he feels that the acceptance of the Mental Health Act by the public and the Press shows that we are shedding old prejudices and fears. But we have still many shortcomings and gaps, and we clearly have much to learn from Mr. Robinson's candid account of his travels.

1. Shaw, D. B., Simpson, T. *Quart. J. Med.* 1961, **118**, 135.
2. Simpson, T. *Lancet*, 1957, ii, 105.
3. Patterns of Care. 1961; pp. 42. (Obtainable from the National Association for Mental Health, 39, Queen Anne Street, London, W.1. 2*s*. 6*d*.)
4. Baker, A., Llewelyn Davies, R., Sivadon, P. W.H.O. public health paper no. 1. Geneva; 1959. See *Lancet*, 1960 i, 965.

Special Articles

SOME MEDICO-SOCIAL PROBLEMS OF REHABILITATION *

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IN 1954 Ferguson and McPhail [1] produced a report on patients discharged from medical wards in hospitals in the West of Scotland, which showed that after three months 33% of those of working age had not returned to work. Two years later, 22% had still not done any work since leaving hospital. The lack of interest in these figures has always puzzled me. Though many papers are published on the treatment of different diseases, they fail to tell you what sort of life the patients eventually lead; and indeed this information is seldom included in hospital records.

At Garston Manor we were curious to see the results of our own treatment and to see what problems our patients met. Accordingly we followed up the 381 patients who were discharged during 1958. We found that by the end of 1959, 245 were working.

Of the others 44 were in need of sheltered work or day centres; 41 had returned to hospital; 37 were not working but were waiting to be found jobs near their homes; 7 had retired; 5 had refused work; 2 were awaiting the result of compensation claims.

THE PATIENT'S PROBLEMS

Of those who were not working, we considered that 44 were capable of doing so. The reasons why they had not taken a job were instructive.

Finance

Of the 5 who had refused jobs, 4 said that they would have been worse off financially. By the time they had paid for fares and meals, they would have less money than their allowances from various sources.

A case can be made out, I think, for the supplementation of earnings. If a man's earning capacity is £7 a week and the rate for the vacant job is £10 a week, it would pay the State to give the £3 balance to the employer. Both for the man himself and for the State, it is better that he should work, and as a worker he would cost the State £3 a week instead of about £8 in allowances.

Compensation

A compensation claim sometimes delays recovery. There is an unfounded belief that a patient should not return to work until his case has been settled. I explain to patients that they have a legal duty to return to work as soon as possible, and that if the work they return to is less well paid than their pre-accident job the compensation is likely to be more. In 2 patients the anxiety and emotional symptoms associated with their legal cases were so severe that return to work could not be achieved.

Date of Starting Work

As confidence gained in the rehabilitation workshop can quickly be lost outside, it is best that the date for starting work should be arranged before the patient is discharged. This is particularly important in patients who have had severe head injuries and who have the curious lack of confidence that goes with this condition.

One man, who had been working quite well in our workshops, I discharged before arranging a starting date with his firm. Within a few days of discharge, his headaches and loss of confidence became severe again and it was a year before he went back to work. Another had to wait about three months at home for his training. Again, his symptoms returned; he did not complete his training, and it was another few months before he went to work as a storekeeper.

The patient's family often unintentionally makes this peculiar lack of confidence worse. A van boy, whose return to work we had arranged for the Monday after his discharge on a Friday evening, was told by his mother that he should not go back to work. It was only the excellent cooperation of his own family doctor and industrial medical officer that kept that boy at work. After a week, his mother was convinced and there was no further trouble.

A housewife was said not to be capable of running her home. We found that her husband did not allow her to do anything at home. After demonstrating to the husband what she could do in the remedial kitchen and how she had managed in Watford with shopping lists, she went home to run her own household again.

THE DOCTOR'S PROBLEMS

As medicine becomes more specialised and more scientific, it becomes difficult to think of the patient as a whole human being. Yet it is important to do this before the patient's discharge from hospital. This is not always easy. The harassed registrar seeking a bed for an emergency only looks for someone fit to send home. This applies particularly to special units which admit patients from, and discharge them back to, general hospitals.

A heavy-lorry driver had a subarachnoid hæmorrhage and was admitted to a general hospital. From there, he went to a neurological centre where, by brilliant surgery, the aneurysm was clipped off. He made a good recovery except for some loss of his visual fields. He was discharged back to his general hospital, where he was told that he was unfit for lorry-driving and then discharged to his family doctor. He was asked to attend the neurological centre every six months, but no comment on his future was made by the general hospital.

He stayed out of work for two years. Because his partial sight was not likely to deteriorate during the next four years, the blind welfare organisations did not follow him up. We found him to have good central vision, to be skilful with his hands, and to be capable of training in light engineering. The Ministry of Labour trained him and found him work with no difficulty.

The moral here is lack of communication between different medical units and other social authorities. What is self-evident to one group is not self-evident to another. The man with a subarachnoid hæmorrhage and partial sight does not sound like a trainee to the Ministry of Labour.

Medicine is so specialised that professional team-work is now a necessity for good results. This means that one of the consultant staff must accept responsibility for the medico-social work in a hospital. It is desirable that the family doctors should keep an eye on the rehabilitation of their patients as far as possible. But the hospital should always give guidance about the future for patients who have to change or modify their jobs. For some it may be necessary for the hospital to arrange for assessment and training, for the amount of paper work can be far more than the family doctor can cope with.

As far as practicable, patients should be assessed in the hospital. This avoids overloading the Ministry of Labour industrial rehabilitation units and so causing long waiting-lists. The ministry of Labour disablement resettlement officer (D.R.O.) is a most useful and helpful person. He is not seen often enough in the hospital. This is the hospital's fault. Mostly after an assessment period in the hospital workshops and an interview with the D.R.O., a

* Based on the Horder memorial prize lecture, for 1961, of the British Spas Federation.

1. Ferguson, T., McPhail, A, N. Hospital and Community. London, 1954.

suitable job or training can be found. Decisions about training should be taken early in a patient's convalescence to avoid unnecessary delays in starting. A three-month wait for a vacancy can be disastrous for morale. If necessary, the patient should continue to attend the hospital rehabilitation department until there is a vacancy. Patients should never be discharged to the care of their doctor with a recommendation that they return to light work. There may be no light work in their industry. If a man's job has to be modified, the hospital should get in touch with the firm's medical officer or works manager and find out whether this is possible. If it is, then the family doctor can arrange the date of starting work. If it is not then the man must continue to attend the hospital for treatment until he is fit, and should see the D.R.O. with a view to finding a job in a more suitable trade.

THE COMMUNITY'S PROBLEMS

Among our patients, 37 could not work because they could not find suitable jobs near their homes. Another 44 were considered fit only for sheltered work.

The Poor Law Act of 1601 laid down the admirable principle that, when work was not available, the local authority was to provide it—buying raw materials for the purpose if necessary. Since the final repeal of the old poor-law, this principle has been forgotten. The public, and sometimes I think, the authorities themselves, seem to be unaware that both the National Assistance Act of 1948 and the Disabled Persons Employment Act of 1958 allow local authorities to establish sheltered workshops.

As to the need for these, figures are difficult to come by. In my own area only about 6 people were classified on the local register as suitable for sheltered work. But we have to remember that a man on the unemployment register has to visit the labour exchange at least twice a week to sign on and (on one of these visits) draw his money. Most doctors are rightly reluctant to sign people as fit if this means that they have to make a difficult journey to the labour exchange to sign for sheltered work in a workshop which the doctor knows is non-existent. The doctor prefers to sign the patients as sick, so that the money-order can be sent to the patient by post. That this becomes a vicious circle is easy to see. If people are not known officially to the local authority or to the Ministry of Labour as requiring sheltered work, no action is taken. When we inquired of our local voluntary societies and of the hospitals and doctors, we found over 60 people in every way suitable. To qualify for a sheltered workshop, a patient must be able to manage 40–44 hours a week; and there are even greater numbers of people who are only fit for a few hours' work a day. Under the National Assistance Act a local authority can provide day-centres or social clubs for them if it wishes to do so.

I am not advocating a new national organisation to deal with sheltered work. Remploy, with 96 factories, already employs about 6000 people. But national organisations are not flexible enough to deal with local problems. I suggest that in each area, the medical services, the Ministry of Labour, employers' organisations, trade-unions, and the voluntary societies get together and find out how many people need sheltered work and day-centres. They can then consider what simple work can be spared from local industry, how people can get to and from the workshops, and where is the best place to site these? In this way a local community service could be started. The people working in the workshop would feel that the local society had an interest in them and affection for them.

Carlyle once said that " Work is the grand cure of all the maladies and miseries that ever beset mankind ".

We discharged a man in 1958, who had a left hemiplegia due to a carotid-artery thrombosis. He had enough skill to train as a one-armed electric welder. The Ministry of Labour, however, would not train him, because there was little prospect of a job in his home area. He has not been found a job since that time. He goes to the park in the morning and for another walk in the afternoon. He visits the labour exchange twice a week. He gets fed up with himself. He draws £8 a week in benefit. The best money can do is to keep him miserable in comfort. It cannot make him feel that he is useful, and that there is a place for him in the community.

The other great social problem is the complexity of the authorities and legislation. For a start, many of the patients do not understand the various National Insurance forms. The amount of paper work needed to help some of them can be considerable.

A patient with bilateral leg amputations recovered well from the operations and learned to walk with his limbs. His firm was anxious to have him back, but there was the journey to and from work. He was eligible for an ' Invacar ', but he lived in a first-floor flat and there was no garage. The local housing authority was unable to rehouse him and the county authority saw no prospect of so doing in the next 5–7 years. The Ministry of Health would not grant the invacar for lack of a garage, which is the local authority's responsibility to erect. There was an impasse. Then it was suggested that the Ministry might supply an old invacar until the man was rehoused with a garage. The only place where the old invacar could be left at night would be the street, but would the police allow that? The local superintendent would allow it until he was rehoused, so long as there was a red light by it at night. In their kindness, neither the Ministry nor the police asked how long the rehousing was likely to take. The man is working now, but the pile of correspondence about him grew to a great size before this was achieved.

The trade-unions too, can be very rigid.

An amputee had an ununited fracture of his left humerus. He returned to his job as a machine-operator and he was such a good operator that his firm wished to promote him to a bigger machine. This meant some lifting which he could not do because of the false joint in his left arm. The firm were prepared to give him another man to help. The union would not agree because (it was said) the agreement between the firm and union was that one man should work that sort of machine. I went to a meeting to say that the disability was genuine and that help was reasonable. The union officers looked sheepish, but would not agree to the man's promotion.

CONCLUSIONS

The aims of the hospital and other social welfare services should be more clearly defined, and the Ministry of Health should be vigorous in seeing that these aims are achieved.

The hospital service must cooperate more closely with other social services, and in particular with the Ministry of Labour, the family doctors, and the local-authority services. The consultant staffs of hospitals must take a greater responsibility for the future of their patients, and one of the consultant staff should have charge of the medico-social work of the hospital.

" To conquer an acute disease is but the first step towards recovery; the health and strength which were sacrificed in the struggle have still to be restored, and this is often the most important stage in the treatment. No hospital can be reckoned at all to fulfill its proper function unless it is provided with some means of treating this second stage of sickness."

The *Times* made this plea for organised convalescence or rehabilitation in a leading article in 1867. Have we made so much progress in achieving this?

Central and local authorities must realise that their regulations and rules are complex and difficult to understand, and indeed unintelligible to many people. These rules and regulations were made for man and must be interpreted for the wellbeing of the patient.

Local authorities must show a greater interest in the care of their communities. The number of sheltered workshops and day-centres opened since 1948 is pitiful.

If we are determined to have integrated hospital and community-care services, we shall get them. We have a great social history behind us. We have to regain the tolerance and affection for each other that the Industrial Revolution did so much to destroy. In the past, most of our great Acts of Parliament were based, like our Common Law, on Christian doctrine. The Poor Law Act of 1601 was based in the principle "Thou shalt love thy neighbour as thyself". We forget this to our peril. It was forgotten in Victorian times and replaced by Benthamite philosophy—the greatest good of the greatest number. This led to great misery and hatred of the poor-law.

The State has given us great powers for good in the National Health Service Act, the National Assistance Act, the Disabled Persons' Employment Act, and the National Insurance Acts. We have to see that these Acts are used to the full and interpreted with charity; for without charity there is nothing.

Points of View

ADVERTISEMENTS FOR HEALTH
A Plea for Truth

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FEW will deny that advertising is desirable and necessary in order to spread information about what is available. What is causing widespread concern, however, is the increasing use of "persuasive" methods, whose aim is to reduce the consumer's ability to choose rationally. The best-known book decrying these methods is Vance Packard's *The Hidden Persuaders*, which calls itself "An introduction to the techniques of mass-persuasion through the unconscious".[1] Recently Ernest Dichter has written a reply which describes itself as "an exciting and authoritative description of the science of persuasion".[2]

A typical defence of modern advertising methods[3] is that (1) advertisers find it profitable and (2) the public likes it. Dichter goes further. He maintains not only that people like advertising but also that they like to be influenced—rather than have to make up their minds for themselves. Moreover, it does them good: for "every new acquisition represents an enrichment of our personality". What motivation research really does, according to Dichter, is to provide a bridge between the consumer and the manufacturer, teaching the latter that his salvation lies in technological advance and in satisfying the real needs of the consumer. "Our role, then, as scientific communicators, as persuaders, is one of liberating these desires, not in an attempt to manipulate but in an attempt to move our economic system forward, and with it our pursuit of happiness."

1. Packard, V. The Hidden Persuaders. London, 1957.
2. Dichter, E. The Strategy of Desire. London: Boardman. 1961. Pp. 320. 25s.
3. Pemberton, A. *Listener*, March 30, 1961, p. 573.

IMPLICATIONS FOR MEDICINE

What are the possible consequences of all this for doctors and their patients?

First of all, the disregard for and distortion of scientific truth found in so much commercial advertising is in fundamental disagreement with the aims and principles of our profession. All around us medical theories and medical practice are recommended, misinterpreted, or ignored for the sake of selling more goods. Sometimes advertisers seek medical practitioners who will, for considerable remuneration, condone or recommend in public the particular product that is being put across. They may even band together to do this.

Recently a public-relations firm representing a number of different interests telephoned a medical practitioner to say they wished to "promote" big breakfasts. They wanted a medical article describing how important it is for health to eat a big breakfast. The doctor replied that in his opinion this was not universally true. He thought that some people could certainly do with eating more breakfast, whereas others could do with less, and he offered to write an article giving his honest opinion. He was then asked whether he could write only about people who ought to eat more, without mentioning the rest. He declined and was told that they would find someone else.

In the House of Commons, Mr. Francis Noel-Baker[4] has drawn attention to methods of advertising so-called health foods, toothpastes, drugs, and patent medicines. The health of the nation, he suggested, was being endangered by dishonest claims made by the manufacturers of these products; and we could certainly agree that many of the products advertised with false or pseudo-scientific theories do not act in the way suggested in their advertisements, or, if they do, they are no better than other substances obtainable at a fraction of the cost.

Some patients are astonished to hear that buying good food is better than buying expensive vitamin supplements, or that, for replacing "lost energy", ordinary sugar is as good as any expensive glucose drink—because the fact that it is not quite so rapidly absorbed is of no practical importance. The public is told that it needs a fresh supply of vitamin C every day; but it is not told that this can come from an orange.

Much of this kind of advertising may be said to do no harm except to the pockets of those who succumb to it. But it is often directed at the least educated section of the community and at the older age-groups, because these most need relief from minor ills. If they waste their money on other things, old people on pensions may not be able to buy enough good food to keep themselves in health. In this way, vicious circles are easily formed. Nobody's health will improve if instead of buying meat and vegetables he buys glucose or vitamin tablets, or tries expensive methods of improving his sight without using glasses, or spends a lot on remedies for falling hair. The London School of Hygiene and Tropical Medicine[5] reported that D.P.H. students investigating chronic bronchitis were impressed by the continued search for costly patent medicines which was a feature of the home life of certain sufferers. Though it is said that such searching brings new hope and is psychologically beneficial, not everyone will agree.

The time-honoured advertisers' argument that they are only giving people what they want is difficult to justify here. It is even more difficult to justify in certain other fields where advertising is liable to do direct harm.

4. See *Lancet*, 1958, i, 1182.
5. Report on the work of the school during the year 1956–57.

DRUGS

The increasing use of habit-forming drugs gives rise to much concern. Though the Advertising Association [6] says that it has no evidence that the increase is due to more advertising, the Interdepartmental Committee on Drug Addiction think it must be partly due to " the vigorous advertising of these drugs and their preparations by the pharmaceutical industry, both to the medical profession and to the public ".[7] Commenting on this advertising, the *Guardian* [8] remarks:

" The lay press (including this newspaper) is more and more bombarded with publicity hand-outs and invitations to press conferences. The greater success the public relations officers of these firms attain, the more ordinary newspaper-buying patients will pester their doctors to let them try the newest remedy they have read about."

Drugs acting on the central nervous system are not the only ones that can do harm: the enormous consumption of laxatives, stomach powders, aspirin preparations, and antiseptic creams, for instance, is something few doctors think wise. The extent and effects of self-medication are not known,[9] but it has been suggested that the annual global injury and number of deaths due to poisoning (excluding alcohol, hashish, opium, and other addictions) exceeds by far the destruction which would be caused by an annual atomic bomb explosion in a built-up area.[10]

ALCOHOL

One of the largest crime increases from 1959 to 1960 was in numbers of convictions for drunkenness, which increased by 3000 or 4%.[11] The figures for buying or trying to buy drink under-age are even more disturbing. In one year, from 1959–60, convictions for buying (or trying to buy) drink went up by 44% for boys and 68% for girls. Among boys, convictions for buying drink are twice as numerous as for drunkenness, while among girls they are fifteen times as numerous. " This gives an indication of the size of the iceberg that lies under the surface of the simple drunkenness statistics." [12]

The cause of these changes is certainly complex; but we must note that they have coincided with what appears to be a special drive to encourage young people to start drinking. Contemporary advertisements for alcohol associate it with manliness, youth, beauty, popularity, and honeymoons—all of which are of special interest to the teenager. When the Advertising Inquiry Council asked an economic statistician to assemble all the available facts, many people were disturbed by the resulting booklet,[13] and particularly by the attempts being made to increase the national consumption of alcohol, especially among the young. The fact that the treatment of alcoholism, once established, is notoriously difficult and unsatisfactory, makes the situation even more serious.

FOOD

What some of the biggest advertisers are trying to do to the nation's diet is also likely to trouble anyone who cares to study it. Emphasis is laid largely on carbohydrate foods, particularly sweets, and there is considerable evidence that the increase in sugar consumption (which rose from 88·3 lb. per head in the United Kingdom in 1948 to 120·7 lb. in 1958) is directly connected with the rapid and deplorable deterioration that takes place year after year in our children's teeth.[14] On the one hand, the school dental service is almost overwhelmed by the work of filling or extracting carious teeth, while on the other hand children hear with monotonous regularity, " Don't forget the fruit gums, mum," and are perpetually reminded of " the sweet you can eat *between* meals ".

Obese people are sitting ducks for anyone who will tell them (or even hint) that they can become slim without personal hardship and without radically changing their eating habits. Though some genuinely helpful preparations have been marketed to help overweight people, so much of the advertising in this field is misleading that probably more harm than good has been done. Packard [2] describes how Dichter deliberately mapped out a programme for the sale of candy, using the idea of the " scientific nibble " of sweets to control appetite! It may be true that some chocolates have " less fattening centres "; but the effect of such an advertisement is that people who wish to slim eat them when they shouldn't. Many varieties of bread and crispbreads have advertisements which *suggest* that by eating them you will grow slim: some patients even deduce that the more they eat, the slimmer they will get. Recently a hypothesis which in medical circles is still at the stage of discussion has been widely adopted by those selling slimming preparations. It is the hypothesis that " fat isn't fattening " and that only carbohydrate is fattening. The result is a plethora of " starch-reduced " substances, many of which have in fact just as high calorific content as their carbohydrate counterparts.

SMOKING

Few medical men now doubt that cigarette smoking is a causal factor in much disease of the lungs. Deaths from carcinoma of the lung continue to increase, so that nowadays about 52 people die from it every day, compared (for instance) with 16 on the roads. Chronic bronchitis—a disease that is rare in those who have never smoked—kills about 30,000 people annually and disables many more. Yet the sales of tobacco continue to rise. Yearly expenditure on it in England, Scotland, and Wales is now over £1000 million pounds, and the tax on this produces annually more than the cost of the whole National Health Service. Nevertheless the vast advertising campaign continues, and again it seems to be directed particularly at young people. More and more children are taking up smoking, sometimes at a very early age; and the habit, once formed, is notoriously difficult to break.

When Francis Noel-Baker drew the attention of the House of Commons to tobacco advertising,[15] the Minister of State, Board of Trade, pointed out that the Government had agreed that the facts about smoking should be brought to public notice. He did not think he had ever seen any advertisement actually saying that smoking was good for one, and he did not believe tobacco advertising was persuading non-smokers to smoke.

The Joint Tuberculosis Council [16] questions whether it is really in the public interest to allow unrestricted advertisement of a substance which reliable evidence suggests is dangerous to health; and in some countries—for example, Sweden since 1956—the advertising of cigarettes and tobacco is prohibited. But in this country nothing

6. *J. advertis. Ass.* 1960–61, **8**, 23.
7. Ministry of Health. Drug Addiction: report of Interdepartmental Committee. H.M. Stationery Office, 1961.
8. *Guardian*, May 25, 1961.
9. *Brit. med. J.* 1960, ii, 1864.
10. Locket, S. Clinical Pharmacology. London, 1957.
11. *Times*, July 28, 1961, p. 7.
12. Christian Economic and Social Research Foundation: 8th annual report. 1961.
13. Advertising Alcohol. Advertising Inquiry Council, 1960.
14. The Health of the School Child. Report of the Chief Medical Officer of the Ministry of Education, 1958 and 1959. H.M. Stationery Office, 1960.
15. *Lancet*, 1958, ii, 1183.
16. *Tubercle*, 1960, **41**, 290.

more has been done than to bring the figures to the notice of the public—a drop in the ocean compared with the enormous pressure of commercial advertising. Unfortunately, a considerable proportion of the national income depends at present on this state of affairs continuing. Legislation against the sale of cigarettes to young people is inevitably ineffective, and slot machines make them available to any child. Meanwhile, the Central Health Services Council, in its report this year on Human Relations in Obstetrics, deplores the absence of facilities for smoking in maternity hospitals!

IDEAS OF HEALTH AND DISEASE

Modern advertising also contains clear messages about the nature of health and disease in general. Much of it promotes the idea that taking drugs is part of normal living, particularly for children and the elderly. It also carries the implication that every little symptom and every little deviation from the average has its specific remedy which should be instantly applied without effort or inconvenience on the part of the sufferer. But perhaps worst of all is our acceptance of all this. Even if we do not accept the philosophy behind the persuasion, we come to accept it as quite reasonable that we should be surrounded and bombarded by it. There are even toy medical outfits on the market which contain " get fit " pills: these are coloured sugar sweets " to replace lost energy ". Recently a 9-year-old child confided in his mother that he was saving up to buy her a box of tablets for her birthday.

Naturally enough, patent medicines are most widely used and advertised for conditions which the medical profession cannot or does not cure. Fifty years or so ago there was an abundance of advertisements for diseases such as diabetes, anæmia, and fevers; and it was probably the discovery of specific pharmacological remedies as much as legislation that led to the decline of such treatments. Today the bulk of medical advertising to the lay public continues to be for conditions for which we have no specific pharmacological cure. But the big difference is that many of them could be prevented, or their prevalence greatly reduced, by public-health methods and by education. This cannot be achieved, and can scarcely be begun, so long as commercial advertising is in opposition to it.

Patent medicines doubtless played a valuable part in the days when people could not afford to visit doctors, and also in raising the standards of personal hygiene. But nowadays, with few exceptions, they are little more than an anachronism, and because of the way in which they are advertised they are often harmful anachronisms. They may save the doctor a bit of work, but probably give him more in the long run. The one field in which direct advertising to the lay public is probably to some extent beneficial is in baby foods. These are often sold along with a good deal of advertising material which is mostly informative rather than persuasive, though unfortunately much of it is some ten or twenty years out of date.

EXISTING CONTROLS

What is being done about it? There is of course legislation, which increases slowly. There are also bodies whose job it is to examine claims made by advertisers, and these bodies have laid down strict rules and codes of standards. Most large advertising agencies employ a medical adviser who is consulted whenever the question of advertising any medical claims arises. Most manufacturers of medical or semi-medical products also have their own scientific advisers, and they often have qualified medical advisers as well. The medical adviser of one of the advertising agencies has even claimed that it is " practically impossible for exaggerated benefits to be claimed in normal advertising channels for ' useless products '." [17] Yet if we but open the nearest newspaper or switch on the television or open the letterbox, the evidence of our eyes belies this statement—unless we forget that what is *suggested* is more important than what is actually *said*.

Chalke [18] has contrasted the enormous expenditure on commercial advertising with the lack of means available for disinterested health education.

Gradually, drugs shown to be habit-forming or toxic are being officially controlled. But late in 1960, many years after the toxic effects of one drug had first been reported and after widespread protests in both Press and Parliament led to its being at last put on schedule, the advertisers were still sending out copy to doctors quoting a medical opinion that it is a safe and effective drug " provided that the dose is not excessive "—but never mentioning the fact that its worst danger is addiction, in which excessive doses are almost always taken to maintain the effects.

The Independent Television Authority is under statutory obligation to set up an advertising advisory committee and to see that its recommendations are carried out. In the booklet *Principles for Television Advertising*,[19] a section sets out a code requiring that no advertisement should contain a claim to cure any ailment or should directly or by implication mislead or depart from the truth on the composition, character, or action of the medicine or treatment. But in the House of Lords last March Lord Taylor was able to recite a series of examples of misleading claims or presentation which he considered to be a manifest breach of the regulations. The selection of advertisements and their approval, he pointed out, was in the hands of the people who make the money out of the advertisements—the programme companies. There was an advisory committee in the background but it had no power and worked retrospectively.

THE DOCTOR'S CONTRIBUTION

There are a number of ways in which, both as a profession and as individuals, we can help to remedy the situation. First of all we can get it clear in our own minds by observing what goes on. A careful scrutiny of advertisements and a comparison of what they say, what they *suggest*, and how this compares with what we wish for our patients and for the community in general can be a revelation. It is not even necessary to seek out the advertisements. They automatically come one's way in newspapers, magazines, and television programmes.

After doing this, it is of considerable interest to study our patients with advertising in mind—first of all, as to how far their outlook on health and disease is conditioned and coloured by the advertisements and secondly as to the extent to which they indulge in patent medicines and quack treatments. If the confidence of the patient is obtained, his revelations will often be fantastic. And not infrequently the cause of obscure and often long-standing symptoms suddenly reveals itself as poisoning by some patent medicine; or the fat patient's failure to lose weight while on a strict diet turns out to be due to believing something that was stated (or suggested) in an advertisement. Any doctor who takes the trouble to do this will

17. Glover, D. *Brit. med. J.* 1958, ii, 165.
18. Chalke, H. D. *Med. Offr*, March 3, 1961.
19. Independent Television Authority. 3rd ed.: July, 1960.

learn more about his patients, but he may become a sadder as well as a wiser man.

We can also make sure that our own doorsteps are clean, especially as regards such advertising as is under our control. At present our own journals are still carrying advertisements which contain misleading statements and exaggerate the claims of the products they are designed to sell. Many advertisements do not even give the price of the product, though it is pleasing to see that an increasing number do. But none compare this price with the cost of using *B.P.* preparations—except very occasionally when the comparison is favourable to the proprietary product.

It has also been suggested [20] that we should adopt a harsher attitude towards apparently respectable firms who are linked with firms "fanning the flames of public appetite for useless and perhaps sometimes dangerous patent medicines and happily exploiting this public addiction". Again, we could perhaps persuade the drug firms to modify some of the recent trends in their advertising methods—for example, pictures of beautiful women to illustrate some of the grosser physiological functions.[21]

As well as these negative measures, we could take a more positive line. For instance, a journal could publish clearly written critical evaluations of the products it advertises. The products concerned could be grouped around it for easy reference, rather as publishers' advertisements cluster round book reviews. And in evaluating these drugs and in helping other people to do the same, it is important that those of us who are concerned with clinical trials should publish the negative as well as the positive results and everything we know about side-effects and possible complications—even when the trial was financed or aided by a drug firm to an extent that makes us feel a sense of obligation (an arrangement which is in any case undesirable). And those of us concerned in medical journalism, both in professional and in lay publications, can be constantly aware of how easy it is to be "persuaded" unwittingly in any of a dozen different ways.

Perhaps *The Lancet* could be induced to make a positive contribution by reverting to an old custom. More than a century ago an important cause of widespread ill health was food adulteration, including alum in bread and red and white lead in sugar confectionery. For years *The Lancet* waged a "solitary but damaging guerrilla war" on these practices by printing the names and addresses of tradesmen, with the adulterations for which they were responsible. In this way the journal forced the passing of the Adulteration Act of 1860. Perhaps it could now do the same regarding advertisements.

SOME PUBLIC PROPOSALS

These suggestions link with others that have been made about advertising in general. *The Times* has pointed out [22] that truth in advertising, if it is not complete, may be more misleading than fiction, and suggests that the ideal answer to television advertising would be an omnibus "advertisement" or programme in which the viewer sees an independent test of the whole range of products on the market—a televised version of the examinations carried out by *Which?* and *Shopper's Guide*. It is suggested that the truth might then be a little less partial. Benenson [23] points out that regular features devoted to the testing and appraisal of goods are a means of giving the Press a steady source of advertising revenue and increased income from advertising and also a way of improving the quality and reliability of advertisements.

The Advertising Inquiry Council (49, Cresswell Place, London, S.W.10) which has just launched an appeal for subscription members, is deeply concerned about advertising which "blinds with false science" or "manipulates emotions in a way that cannot be to the public good". The first issue of its monthly bulletin [24] remarks that we already have a large number of bodies designed to maintain advertising standards, but they have little standing and less influence. The proposals made by Mr. Sinclair Wood, in his recent presidential address to the Institute of Practitioners in Advertising, that the industry should establish machinery to "prevent the publication or transmission of any advertising which was untrue, misleading or against the public interest" will be no more than additional camouflage unless the members of his Advertising Standards Council include laymen. It is no longer sufficient for the public to be asked to address complaints to a body made up of advertising spokesmen; yet the council proposed by Mr. Wood comprises the heads of each of the major advertising organisations, presided over by "an eminent legal person, approved by the Board of Trade". "Greater direct representation for the consumer's interest seems necessary in view of the fact that advertisers are now spending money at the rate of almost £10 a year for every man, woman and child in the country."

EDUCATION

Another important line of approach is through education. Williams [25] thinks that we should have a public research and information service, with adequate offices and showrooms in every town, where the ordinary buyer could make a genuine choice. The modern system of advertising, he says, is simply a pre-democratic form of manipulation of a public regarded as "masses".

In 1935, Baster [26] suggested that the best way of reform is to make the consumer more aware of the advertising process and its effects upon him. Two years earlier Leavis and Thompson [27] outlined a plan for counteracting the influence of advertising by education. So far as medicine is concerned, this means the education of doctors, of students, and of the lay public. This largely means the spreading of information that is not only true but also, so far as possible, completely true, as well as being easily available and easily understood by those for whom it is intended. Unfortunately, at the moment, the easiest way for doctors to keep up with the latest therapeutic developments is to read the publications of drug firms. All other methods, including reading *Prescribers' Notes* and the new *Prescribers' Journal*, require considerable application and an unusual quality of dedication. And if it is true that what really makes for good prescribing is, among other things, "sound undergraduate education in therapeutics" [28] then there are probably lessons to be learnt from the report lately published by the British Medical Students' Association, on the teaching of pharmacology, therapeutics, and pharmacy in medical schools.

Perhaps such legislation as does exist could be made more effective through lawsuits. There is some precedent for this, at least in America.

20. Taylor, C. *Brit. med. J.* 1959, i, 787.
21. Gover, W. *ibid.* 1961, i, 1466.
22. March 4, 1961.
23. Benenson, P. A Free Press. Fabian Society, 1961.
24. *Scrutiny*, May, 1961, p. 1.
25. Williams, R. Long Revolution: p. 347. London, 1961.
26. Baster, A. S. J. Advertising Reconsidered; p. 127. London, 1935.
27. Leavis, F. R., Thompson, D. Culture and Environment; p. 12. London, 1933.
28. *Brit. med. J.* 1959, i, 1285.

In 1891 a lady developed influenza after a course of 'Carbolic Smoke Ball' and claimed the £100 reward offered by the manufacturers if this happened. When they refused to pay, she sued and won the case.

In 1900, in Chile, a customer bought a preparation "warranted to cure the worst case of toothache in ten minutes". He tried the remedy on the spot, took out his watch, and after ten minutes, finding that he still had toothache, had the agent arrested. The penalty imposed was a fine of 1000 dollars with three months' imprisonment.[29]

More recently, an American cancer patient lost his action against a tobacco company in which he claimed that his cancer was the result of smoking a brand of the company's cigarettes for many years.[30]

Those who are troubled about the effect of present-day advertising on health and disease will mostly agree that further legislation is necessary. There are a number of serious and prevalent diseases which legislation could eliminate as effectively as it has, for example, eliminated cholera and opium-smoking—and with no more curtailment of the freedom of the individual. For freedom itself calls for a corresponding protection against suggestion and "persuasion".

Baster [26] has suggested that the reformer of advertising should use the efficiency of the advertising machine. Dichter [3] himself says that to convince and persuade people to become the controllers of their own lives is possibly another important job for persuasion and motivation techniques. It is interesting to reflect on what the world in general, and the health of the nation in particular, would be like if the Hidden Persuaders, their effective techniques and the organisations that they serve, were dedicated to selling their goods within the limits of the truth, the whole truth, and nothing but the truth. For they do harm only when they disregard and distort the truth for commercial purposes.

29. Turner, E. S. The Shocking History of Advertising; p. 176. London, 1952.
30. *Brit. med. J.* 1960, ii, 474.

Public Health

ROUTINE IMMUNISATION AGAINST INFECTIOUS DISEASES

As a result of advice by the Standing Medical Advisory Committee, combined vaccines are likely to be used increasingly in the future. The advice, contained in a memorandum that is to be circulated to all general practitioners, is as follows:

It is now possible to provide protection against several infectious diseases in early life by active immunisation and there has recently been considerable debate as to the most satisfactory timing of the different immunising procedures. In this context three considerations seem to be of particular importance: (1) the greatest possible measure of immunity should be provided against each particular disease; (2) there should be the least risk of causing harmful reactions or complications and, in particular, of inducing provocation poliomyelitis; (3) the number of injections given to the child and the number of visits necessary should be as low as possible.

No single schedule can fully meet all these considerations, and the two accompanying alternative schedules are different attempts to reach a compromise. Modification of these schedules may be necessary later in the light of rapidly advancing knowledge. Attention is drawn in the following paragraphs and in the notes to each schedule to factors which will be of importance in deciding which schedule is most suitable. In some cases it may be desirable to modify one of the schedules to meet special circumstances.

In general, the ability to form antibodies in response to an antigenic stimulus is immature at birth and may not be fully developed until about six to nine months of age. Although a useful response is to be expected before that age, it may not be maximal. Another factor which may affect adversely the ability of the infant to respond to active immunisation is a high level of maternally transmitted antibody. For these reasons vaccination against poliomyelitis, for example, is deferred until the infant is at least six months old.

SCHEDULE P

Age	Visit	Vaccine	Injection	Interval
2–6 mos.	1	Diphtheria, pertussis, tetanus 1	1	4–6 weeks
	2	Diphtheria, pertussis, tetanus 2	2	4–6 weeks
	3	Diphtheria, pertussis, tetanus 3	3	
7–10 mos.	4	Poliomyelitis 1	4	4 weeks
	5	Poliomyelitis 2	5	
15–18 mos.	6	Poliomyelitis 3	6	
18–21 mos.	7	Diphtheria, pertussis, tetanus 4	7	
Smallpox during first 2 years but preferably at 4–5 mos. (see note *h*).				
School entry		Poliomyelitis 4, diphtheria, tetanus		
8–12 yr.		Diphtheria, tetanus, smallpox re-vaccination		
Over 12 yr.		B.C.G. (see note *i*)		

NOTES

(*a*) Pertussis vaccine is given early in the hope of reducing the incidence and severity of whooping-cough in infancy.
(*b*) There is no real need to give diphtheria and tetanus toxoids so early in life as the incidence and death-rates from those diseases below the age of a year are almost negligible.
(*c*) The use of a combination of a bacterial vaccine and two toxoids may increase the incidence of "provocation" paralysis.
(*d*) The first injection is given in early life, at which time the mother is more likely to accept advice about immunisation matters.
(*e*) A practical argument for this schedule is that it is at present being used (possibly with minor modifications) by a number of local health authorities and general practitioners.
(*f*) The number of visits and injections is greater than in schedule Q.
(*g*) Should it be desired, visit 7 may be avoided by giving poliomyelitis 3 and diphtheria/pertussis/tetanus 4 at different inoculation sites during visit 6.
(*h*) An interval of at least two weeks should normally be allowed to elapse after an injection of diphtheria/pertussis/tetanus or poliomyelitis vaccine before undertaking vaccination against smallpox. When vaccination against smallpox precedes an injection of one of the other vaccines it is desirable to allow at least three weeks to elapse.
(*i*) B.C.G. vaccines may be given to schoolchildren aged 10 years or more, at the discretion of the medical officer of health.

SCHEDULE Q

Age	Visit	Vaccine	Injection	Interval
6–8 mos.	1	Poliomyelitis 1	1	4 weeks
	2	Poliomyelitis 2	2	
9–12 mos.	3	Diphtheria, pertussis, tetanus 1	3	4–6 weeks
	4	Diphtheria, pertussis, tetanus 2	4	
15–18 mos.	5	Poliomyelitis 3	5	
18–21 mos.	6	Diphtheria, pertussis, tetanus 3	6	
Smallpox during first 2 years but preferably at 4–5 mos. (see note *f*).				
School entry		Poliomyelitis 4, diphtheria, tetanus		
8–12 yr.		Diphtheria, tetanus, smallpox re-vaccination		
Over 12 yr.		B.C.G. (see note *g*)		

NOTES

(*a*) On this schedule, no antigen is given *by injection* before the age of 6 months, which increases the possibility of a maximal antibody response.
(*b*) Two doses of poliomyelitis vaccine are given before any other injection and, although it cannot be accepted as proven, this might well reduce the risk of "provocation" paralysis which would otherwise be increased owing to the use of the combination of pertussis vaccine with toxoids.
(*c*) Vaccination against pertussis is delayed until between 9 and 12 months; thus no direct protection is offered against the risk of death among younger infants. On the other hand, the time of vaccination in this schedule is nearer to the time of maximum incidence of the disease and this may indirectly protect infants by reducing their chances of being infected by older children.
(*d*) The number of visits and injections is smaller than in schedule P; but possibly if immunisation is postponed until the baby is 6 months old, it may be less easy to gain the continued cooperation of the parents. Early vaccination against smallpox would, however, help to keep the mother in touch with the doctor.
(*e*) Should it be desired, visit 6 may be avoided by giving poliomyelitis 3 and diphtheria/pertussis/tetanus 3 at different inoculation sites during visit 5.
(*f*) An interval of at least two weeks should normally be allowed to elapse after an injection of diphtheria/pertussis/tetanus or poliomyelitis vaccine before undertaking vaccination against smallpox. When vaccination against smallpox precedes an injection of one of the other vaccines it is desirable to allow at least three weeks to elapse.
(*g*) B.C.G. vaccine may be given to children aged 10 years or more, at the discretion of the medical officer of health.

The use of combined antigens requires a careful balance between them in order to prevent the response to one antigen overwhelming that to other antigens. The manufacturers of combined antigens recognise the importance of this.

It has been shown that the use of certain combined antigens (for example, a combination of pertussis vaccine and diphtheria toxoid) carries a slight risk of provocation poliomyelitis—i.e., poliomyelitis occurring within a few days of injection with paralysis particularly affecting the site of inoculation. However, the risk of such cases is much less than in past years, and there is reason to believe that they will not become more frequent if the prevalence of poliomyelitis in the population remains low. The objection on this ground to the use of combined antigens is therefore considerably reduced.

It is a reasonable assumption that poliomyelitis vaccination will protect against provocation paralysis although this has not been demonstrated in man.

The number of deaths from whooping-cough has been falling very considerably for several years. Deaths after the first year of life are rare. The majority of deaths occur in the first six months of life, so that even very early immunisation is unlikely greatly to reduce these deaths. The time of maximum incidence of the disease, as judged by notification figures, is from one to four years.

In general, there are advantages in immunising children at a time which would ensure that their resistance to infection will be at its height when the risk of exposure is greatest. It is possible, however, that a mother can be more readily persuaded to accept immunising procedures if the first approach is made early in the child's life.

It is considered desirable to offer immunisation against poliomyelitis at about the age of seven or eight months with a reinforcing dose after the fourteenth month, against diphtheria between nine and twelve months with reinforcing doses after the eighteenth month and before school entry, and against smallpox at four to five months. Immunisation against whooping-cough may be started either in the early months of life or towards the end of the first year—before the time of maximum incidence of the disease. It seems unlikely, in view of the relative mildness of whooping-cough after the first year, that reinforcing doses are indicated against this disease. It will also be desirable to offer immunisation against tetanus in the first or second year, with a reinforcing dose before school entry. These points are discussed in more detail in relation to each of the schedules.

Poliomyelitis in Oldham

A TOTAL of 13 cases of paralytic poliomyelitis have been confirmed in Oldham and adjacent districts in recent weeks. Only 1 vaccinated child has had the disease. A second dose of vaccine had been given on Aug. 1, eight days before the child fell ill. Paralysis was mild and it is expected that little or no post-hospital treatment will be necessary. A man of 35 died on Aug. 30. His illness was preceded by a period of considerable physical effort, and paralysis was rapid and progressive. He had had one dose of vaccine about two weeks before the onset of symptoms.

We are indebted for this information to Dr. J. T. Chalmers Keddie, medical officer of health for Oldham.

Suspected Smallpox

A zoology student living at Tenterden in Kent returned last week from a holiday in the South of Spain, and later he went to Ashford Hospital because he had a rash. He had no fever or other signs of smallpox, but, while the tests were completed, he was moved to Long Reach Hospital, Dartford, and vaccination was arranged for the hospital staff and for customs and passport officials with whom he may have been in contact at Dover. Passengers who came from Ostend on the *Reine Astrid* on Sept. 8 were advised by the Ministry of Health to consult their doctors about the advisability of vaccination. As we go to press, we learn that laboratory tests for smallpox have proved negative.

Conferences

EMERGENCY RESUSCITATION

A SYMPOSIUM on Emergency Resuscitation was held in Stavanger, Norway, on Aug. 21-24, under the chairmanship of Prof. RONALD WOOLMER (London). It was sponsored by the Norwegian Association of Anæsthetists, and its eighteen members came from Norway, Sweden, Denmark, Great Britain, the U.S.A., Canada, France, West Germany, Austria, and Switzerland. In addition, about seventy observers were present. They came from a dozen countries, and represented the armed forces, civil-defence organisations, the Red Cross, St. John Ambulance Association, accident services, and public-health and educational authorities.

Dr. KARL EVANG, the Norwegian Minister of Health, who opened the proceedings, pointed out that this arrangement marked a new departure in communication; for though the symposium was confined to a manageable number, the presence of observers from so wide a field ensured that reports of it could be carried immediately to those interested in many parts of the world.

Two days were devoted to scientific discussion. Respiratory resuscitation and drowning were considered on the first day, and cardiac resuscitation and combined cardiac and respiratory resuscitation on the second day. On the third day questions from the observers were answered by members of the symposium, and on this day the observers participated in the discussion.

A fair amount of new material was presented—notably by Dr. ARCHER GORDON (New Mexico) and Dr. PETER SAFAR (Pittsburgh) on the pathology of drowning—but the emphasis was on the best application of common knowledge. The weight of evidence was overwhelmingly in favour of mouth-to-mouth or mouth-to-nose as the best method of respiratory resuscitation. Only two contraindications appear worth considering: facial injuries and (a very poor second) racial or æsthetic prejudice. This method has already been adopted by the armed forces of several countries, and its adoption by the NATO forces is likely to be considered soon.

Methods of teaching mouth-to-mouth and mouth-to-nose resuscitation were much discussed. One of the most significant contributions was from Dr. BJØRN LIND and his colleagues in Norway. He told of the decision of the Norwegian educational authorities to institute compulsory instruction in mouth-to-mouth resuscitation in primary schools. This involves its teaching to 130,000 pupils between the ages of 12 and 14 this year. A pilot scheme, involving 6900 pupils, was operated in the county of Rogaland last year. In a controlled comparison of a training film and a training mannikin as the means of instruction it was found that, of those instructed by film, 37% were able to pass the test of ability to inflate a model victim with eight or more litres of air in one minute, while of those instructed by mannikin, 73% were successful.

Drainage of water from the lungs of a partly drowned victim received a good deal of attention. Dr. HENNING RUBEN (Denmark) reported experiments on warm cadavers. After water had been introduced into the lungs, it was found impossible by any ordinary manœuvres to recover a significant proportion of it.

Several members presented material on the factors contributing to airway obstruction, and from this it emerged clearly that full extension of the head was the most important factor in avoiding obstruction. The prone position was not superior to the supine in promoting patency of the airways.

The practice, effectiveness, and applications of closed-chest cardiac compression were fully discussed, and a respectable number of cases from Baltimore and Pittsburgh were analysed by Dr. SAFAR. Mr. W. P. CLELAND (London) gave an account of experiences with the method at the Postgraduate Hospital and showed a short film.

Several speakers stressed the importance of integrating respiratory and cardiac resuscitation, since the best artificial ventilation is ineffective without an adequate circulation; and the promotion of circulation is useless without oxygenation of the blood.

At the conclusion of the symposium, the following recommendations were announced (these are couched in general terms because it was felt that they should not include details which would properly form the subject-matter of a training manual):

1. The method of artificial respiration recommended in an emergency is full extension of the head and blowing through the mouth or nose.
2. The immediate start of resuscitation should be given priority over clearing the airway and draining water from the body of the victim.
3. The prone position should not be regarded as superior to the supine position either with regard to patency of the airways or with regard to drainage from the lungs.
4. First-aid workers of all categories, schoolchildren, and the general public should be taught mouth-to-mouth and mouth-to-nose resuscitation.
5. Organisations and individuals concerned with teaching life-saving should try to obtain training aids, which include dolls or mannikins, airway models, films and film-strips, and diagrams and pictures.
6. The use of airways and other adjuncts should be taught only to medical personnel, nurses, and recognised life-savers.
7. External cardiac resuscitation should be taught and used only in conjunction with artificial ventilation, and for the present its use should be confined to medical personnel, nurses, and recognised life-savers.
8. The best way of disseminating the knowledge of artificial respiration would be its compulsory teaching to schoolchildren.
9. A central information bureau should be set up in each country to collect information about incidents occurring outside hospitals in which methods of resuscitation have been applied.
10. The World Health Organisation should be asked to act as an international information centre to collect and classify information from national centres.

A full report will be published in English as a special supplement of *Acta Anæsthesiologica Scandinavica*.

ENDOCRINE SURGERY

FROM A CORRESPONDENT

THE International Society of Surgery held its 19th congress in Dublin on Sept. 2–9, under the presidency of Prof. E. DAHL-IVERSEN (Copenhagen). The main subject was the surgery of the endocrine glands, in particular the adrenal cortex, the parathyroids, the thyroid, and the islet tissue of the pancreas. Little new was reported in the formal sessions, but experience from most parts of the world was shared.

Cushing's Syndrome

Prof. P. FITZGERALD performed an adrenalectomy on a patient with this condition, which was seen on colour television and discussed by a panel. Several large series, treated by adrenalectomy, were reported and R. G. SPRAGUE and W. WALTERS (Mayo Clinic), H. SWAN (Denver), F. GLENN (New York), E. ANGELESCU, I. FAGARASANU, D. STOENESCU, and D. MOTOMANCEA (Bucarest), and D. A. D. MONTGOMERY and R. B. WELBOURN (Belfast) between them reviewed some 300 patients. There was general agreement that the diagnosis of adrenocortical hyperfunction should be made preoperatively, but little discussion of the difficulties sometimes encountered in the interpretation of laboratory findings. It was agreed also that the removal of an adrenal tumour or bilateral adrenalectomy was the procedure of choice for the great majority of patients and that the pituitary should be attacked primarily only in the rare patients with clear evidence of pituitary tumour. There was *dis*agreement, however, about whether adrenalectomy for patients with hyperplastic or hyperfunctioning glands should be total or subtotal. Those who favoured subtotal removal agreed that the *right* gland should always be removed completely because reoperation on this side (if required) may be difficult and hazardous. Total resection was almost certain to cause permanent remission, but demanded indefinite treatment with cortisone and occasionally with a mineralocorticoid as well. Subtotal resection was sometimes followed by recurrence, but obviated the need for replacement therapy in about half the patients. Even those who followed this course recognised that serious, or even fatal, adrenocortical failure may develop at any time, especially in the event of stress, and admitted that there was much to be said for total resection and for accepting from the outset the need for permanent replacement therapy.

Diverse surgical approaches to the adrenal glands were employed. Most surgeons preferred to inspect both glands before resecting one and the films of Swan and of Walters and Sprague illustrated very clearly how this could be done through two posterior incisions (either below or through the diaphragm) with the patient on his face. If a large tumour was found unexpectedly, it might be impossible to remove it by this route. If a tumour was known to be present it should be approached by the lateral thoraco-abdominal route. Some surgeons employed this approach routinely on the grounds that it was the easiest and that, since a preoperative diagnosis of adrenocortical hyperfunction had been made, both adrenal glands must be removed unless one was found to be atrophic.

Hypokalæmia is a fairly common feature of Cushing's syndrome and must be corrected before operation. W. HARTENBACH (Munich) reported that the *muscle* potassium was reduced in 25% of patients before operation and in all patients immediately after, presumably as a result of the combined (protein) catabolic effects of cortisol and of surgical stress. Two previously unrelated phenomena were associated in a unique case reported by A. MONSAINGEON (Paris). Thymic tumours have long been known to be associated occasionally with Cushing's syndrome and it was now recognised that pituitary adenomas continued to grow and to cause clinical effects—addisonian pigmentation, headache, eye signs, &c.—in about 10% of patients after adrenalectomy. In Monsaingeon's patient both pigmentation and a malignant thymoma developed about 2 years after operation and regressed after destruction of the pituitary by yttrium 90.

An association between pelvic tuberculosis and hyperadrenocorticalism (virilism and/or Cushing's syndrome) was illustrated in 4 case-reports by D. K. O'DONOVAN and J. G. DEVLIN (Dublin). A causal relationship was suggested by the fact that the condition may apparently be arrested by antituberculous chemotherapy.

Hyperparathyroidism

Hyperparathyroidism was reviewed by H. KUNZ (Vienna) and about 12 others. While the condition may assume many clinical guises, it was generally agreed that the commonest was that associated with renal stones, and that this was more difficult to diagnose than the osseous type. A pessimistic view was taken of the prognosis even after removal of a tumour or of hyperplastic glands. The prognosis was mainly related to the degree of renal damage, for the bones would heal (albeit with permanent deformity). U. BRACCI (Firenze) reported the findings of extensive deposits of calcium in the kidneys and suggested that routine biopsy of the kidneys during operations for the removal of stones might be helpful in the recognition of hyperparathyroidism. It would probably be unwise to attempt percutaneous biopsy of a possibly calcified kidney.

R. J. COFFEY (Washington) reviewed a series of 20 cases of hyperparathyroidism, several of whom had also suffered from gout. There was a high incidence of postoperative tetany amongst these patients, but *hypo*parathyroidism was a lesser evil than *hyper*parathyroidism. L. GOLDMAN (San Francisco) reviewed 100 cases and emphasised the difficulties in the diag-

nosis. He subjected to operation only those patients in whom hypercalcæmia had been found on three separate occasions. He had found that, in the X-ray diagnosis of bone involvement, changes in the phalanges were more reliable than absence of the lamina dura of the teeth.

M. G. McGEOWN (Belfast) discussed the biochemical tests carried out on 89 patients with hyperparathyroidism, 84% of whom had presented with renal stones. She had found that elevation of the serum-calcium was the most reliable sign of hyperparathyroidism, but that it was usually elevated only intermittently. It was necessary to measure the serum-calcium many times over a period of months. Other tests were less useful because they did not separate clearly hyperparathyroid subjects from euparathyroid patients with renal stones, especially when azotæmia was present. Electrophoresis of the serum proteins and the cortisone test were useful for the exclusion of other causes of hypercalcæmia.

A. O. ADESOLA (Belfast) had investigated the alimentary tracts of the same group of patients and found that a high proportion had duodenal ulcers (23% of the males) or other alimentary symptoms. Almost all of these had been relieved by parathyroidectomy. In some of these patients tests of gastric function had been carried out before and after parathyroidectomy and had shown a significant fall in basal secretion of acid after operation.

NEUROPATHOLOGY

FROM A CORRESPONDENT

THE Fourth International Congress of Neuropathology was held in Munich from Sept. 4 to 8, under the presidency of Dr. WEBB HAYMAKER (Washington). It is significant of the times that almost a quarter of the 208 papers were devoted to electron microscopy and rather more than a quarter to histochemistry. Anatomists are much occupied in studying many still unexplored territories of the fine structure of the normal nervous system; but pathologists, it is gratifying to note, have not lagged behind in their use of this instrument. H. HAGER (Munich), in his closing remarks, was able to speak of " the rich and extensive observations " reported to the meeting.

H. F. DE WEBSTER (Boston) in a study on the demyelination which occurs in experimental diphtheritic neuritis found that the earliest changes amount to focal fragmentation of the mesaxons, the appearance of osmophilic densities in the zones of lamellar discontinuity at the nodes of Ranvier, and focal alteration of the lamellar pattern of the myelin in the layers nearest the Schwann interface. The neuromuscular junction came in for much attention: S. I. ZACKS and coworkers (Philadelphia) noted the effect on it of the botulinus toxin. J. BLUMBERG (Washington), C. COËRS and E. DE HARVEN (Brussels), J. B. FINNEAN and A. L. WOOLF (Birmingham), and others described changes noted in biopsy material from patients with myasthenia gravis and other diseases.

Much progress has been made in unravelling the intricate structure of the neuropil, and S. L. PALAY (Bethesda) was able to report that in the molecular layer of the cerebellum all the known fibre components can now be identified. The cerebral cortex is more complicated; but knowledge is steadily accumulating, some of it being gained with the help of experimentally induced œdema or inflammation. K. NIESSING and W. VOGELL (Marburg) and G. ULE (Kiel) described their findings in cerebral œdema, the former workers making use of biopsy material from human brains and concluding that even in this condition there is no extracellular fluid in the grey matter. Niessing and Vogell noted that a grossly œdematous area might be surrounded by completely normal tissue. J. E. GRUNER (Strasbourg) described swelling of the oligodendrocytes and of the astrocytes, the latter with vesicle formation and the early appearance of gliofibrils, in biopsy material from 14 cases of cerebral œdema. He illustrated also the biopsy findings in two instances of subacute sclerosing leucoencephalitis.

The difficulty of interpreting cortical electron micrographs was raised by J. F. HARTMANN (Minneapolis), particularly in respect of the glial elements. He favoured the view that the low-density " watery " processes belong to astrocytes and not to oligodendrocytes. A study of the synaptic organelles of the central nervous system was reported by E. G. GRAY (London).

A. PETERS (Edinburgh) compared the structure of the myelin in the optic nerve and spinal cord of rats, tadpoles, and frogs with that in the peripheral nervous system. Although the process of myelin formation is evidently similar, the cytoplasm on the outside of the mature myelin sheath in the central nervous system is confined to a small tongue-like process which occupies only a fraction of the circumference of the sheath. The greater part of the sheath therefore is uncovered so that between adjacent sheaths there is no intervening cytoplasm. Myelin formation, however, as in the peripheral nervous system, is on a segmental basis. C. E. LUMSDEN and R. PIPER (Leeds) reported on an electron-microscopical study of dorsal root ganglia, mammalian cerebellum, and schwannomas all of which had been grown in vitro. They had noted more complex situations than had hitherto been postulated in respect of the invagination of axons into Schwann cell sheaths.

H. HAGER described the changes which follow experimentally induced trauma, and he illustrated necrosis of brain tissue. He showed that in the neuropil there may be a total dissociation of tissue components, so that only cell membranes and occasional mitochondria are still recognisable, the former often appearing " soaked " and disproportionately swollen. He thought it probable that the progressive separation of the originally closely associated outer surfaces of cell membranes which he had noted was the equivalent of softening. He illustrated the way in which leucocytes and cerebral histiocytes could migrate into this dissociated tissue. Professor Hager later remarked that after fifteen years in which the electron microscope had been available to us, we were only at the very beginning of our work. He warned, however, about the danger of expecting too much from this instrument in the recognition of early cell changes. Because of the necessity for fixation we were still a long way from a study of living molecular systems.

Those who feel that the electron microscope is perpetuating the static outlook imposed on the light microscopist by the processed block of tissue were rewarded by many interesting presentations in the field of tissue culture. Among the most spectacular was the film produced by C. M. POMERAT (Pasadena) portraying the behaviour of cultured neurones and glia: of particular interest was the activity of the cells comprising the whorls of a meningioma. L. COSTERO (Mexico City) had studied 8 tumours of the carotid body, and his film showed the remarkable capacity of the pyriform cells to extend a solitary process, without collaterals, for a distance of 4 mm. These cells were clearly specialised receptors.

M. R. MURRAY (New York) and her co-workers described a series of very elegant studies which centred on the application of tissue culture to the study of allergic encephalomyelitis. The earliest change appeared to be swelling of the neuroglia, but the myelin sheaths soon reacted with fusiform swelling and distortion, some breaking away to be free of the axon. Nerve-cells appeared little affected and most axis cylinders were intact. One of these studies had to do with a comparison of the distribution of cytochrome oxidase with that of succinic dehydrogenase and diaphorases during myelin formation and maintenance.

H. HYDÉN (Gothenburg) reported on studies with isolated nerve cells from Deiters' nucleus and their satellite cells. After stimulation of the neurone its respiratory enzyme activity increased and anaerobic glycolysis decreased: the oligodendrocyte, however, showed the reverse, indicating the likelihood of a metabolic symbiosis between them. The inference from this extremely fine and delicate experiment was that the nerve-cell appears to demand priority, and this prompted a newspaper to liken the oligodendrocyte to a good housewife. Microelectrophoretic analyses of the ribosenucleic acid formed in the neurone and in the glia under different conditions had produced more direct evidence for this symbiosis.

I. KLATZO and J. MIQUEL (Bethesda) had studied the uptake by various cells of proteins labelled with fluorescein isothiocyanate, concluding that in the white matter the potential extracellular space is readily accessible to it when increased permeability is induced experimentally. Intravenously injected labelled fibrinogen, for instance, was demonstrable in areas of œdema in the form of diffusely scattered threads without obvious spatial relationship to the cellular elements. The astrocytes showed discrete intracytoplasmic inclusions of the protein material, the assumption being that they arrived there by a process of pinocytosis.[1] In the grey matter, on the other hand, the passage of the labelled protein from injured blood-vessels was always confined to the immediate vicinity of their walls, and inclusions in astrocytes were not observed.

N. ALLEN (Chapel Hill) was one of several who had made enzyme studies on tumours. He reported that oligodendrogliomas show a high cytochrome oxidase, and a high dehydropeptidase-1 activity but a very low β-glucuronidase activity. By contrast, well-differentiated astrocytomas had very little of the first, a great deal of the second, and very little of the third. Notably anaplastic tumours of both glial and neuronal derivation tended to have a common pattern of enzyme activity, the content of cytochrome oxidase being intermediate in amount between the oligodendroglioma and the astrocytoma.

L. J. RUBINSTEIN and his colleagues (Bethesda) found that in an area of œdema induced by cold injury an increase of glutamic dehydrogenase activity was observed in the astrocyte within 12 hours, whereas increases in diphosphopyridine nucleotide (D.P.N.) diaphorase, D.P.N.-linked isocitrate dehydrogenase, and α-glycerophosphate dehydrogenase were only apparent at 24 hours. Triphosphopyridine nucleotide (T.P.N.) diaphorase and T.P.N.-linked dehydrogenase activity were increased only after 48 hours. These results seemed to indicate progressive activity of this cell.

W. ZEMAN (Indianapolis) reported results which indicated that after microbeam irradiation, whereas neurones are unable to regenerate, a steady supply of mesenchymal elements can enter the affected area from the neighbouring tissues.

H. E. RIGGS and C. RUPP (Philadelphia) presented their analysis of variations in the form of the circle of Willis to collateral circulation in 994 specimens. In only 19% of instances was the pattern strictly normal. In 5% of cases all components were hypoplastic and relatively equal in size: deformities of this type could provide resistance to a free circulation within the circle, but dynamic imbalance could occur as the result of several of the deformities.

PRESERVATION OF BONE-MARROW

FROM A CORRESPONDENT

A CONFERENCE on this subject was held at the University of Buffalo, New York, on Aug. 18–19.

The effective preservation of bone-marrow is of very considerable interest in view of the application of hæmopoietic infusions to the management of accidental radiation exposure and to the treatment of malignant disease by anti-tumour chemotherapy and wide-field irradiation. Barnes and Loutit [1] showed that the hæmopoietic cells of the infant mouse spleen were effectively preserved at −79°C by the glycerin/slow-cooling technique of Smith [2] and Polge and Lovelock.[3] Much of the work presented at the conference—a direct extension of this observation—was aimed at finding better additives than glycerol. M. A. BENDER (Oak Ridge, Tennessee) reported that mannitol, sorbitol, ribose, lactose, and even calcium chloride in optimal concentrations were all effective, but probably not superior to glycerin; but M. ASHWOOD-SMITH (London) was able to show that mouse bone-marrow preserved in media containing dimethyl sulphoxide surpassed glycerin-preserved marrow when judged by the speed of restoration of the recipient's leucocytes. An in-vitro tissue-culture test of viability indicated that polyvidone was also better than glycerin for preserving rat bone-marrow (V. RICHARDS, San Francisco).

The significance of the various in-vitro viability tests used by different workers was discussed. Most speakers had experience of the dye-permeability test, which was generally agreed to be very misleading. The acridine-orange test, applied to mouse marrow preserved in dimethyl sulphoxide and to human marrow preserved in glycerin, seems altogether more satisfactory. Measurements of enzyme activity (peroxidase and alkaline phosphatase), deoxyribonucleic-acid synthesis from labelled formate or thymidine, fat and protein synthesis, and ^{59}Fe and ^{14}C-formate uptake were all reported, and indicated reasonably good preservation in marrow freshly frozen at 1°C per minute in the presence of glycerin or dimethyl sulphoxide. However, it was felt strongly that heavy reliance should not be placed on any one of these tests; good results in the whole battery would probably be more significant. Much more information is required on the correlation of these in-vitro tests with in-vivo assay in irradiated animals. This is particularly important in the preservation of human bone-marrow, for here the in-vivo test is not practicable. I. IOSSIFIDES (Philadelphia) has attempted such a correlation in the mouse, using glycerin-preserved marrow. In-vivo assay showed no difference between unfrozen and frozen bone-marrow, though morphological examination and isotope-uptake tests on the thawed marrow indicated considerable damage.

The optimum temperature for preservation was also considered. E. D. THOMAS (Cooperstown, New York) reported successful recovery after lethal irradiation in dogs which received an infusion of autologous marrow preserved in glycerin for 14 months at either −79°C or −196°C. M. A. BENDER found in mice that storage at −196°C gave better results after the first year. At the cryobiology laboratories of the Linde Company, A. ROWE and A. P. RINFRET (Buffalo) demonstrated new apparatus for the controlled cooling and low-temperature storage of bone-marrow at liquid nitrogen temperatures (−180 to −196°C).

D. E. PEGG (London) described current methods for preserving human bone-marrow by the glycerin technique; in-vitro tests indicate a steady decline in viability during storage at −79°C. It seems probable that marrow stored at this temperature for longer than 2 years would be of little use clinically. J. AMBRUS (Buffalo) reported encouraging clinical results of treating malignant disease in man with a conjugated mustard, in conjunction with β-aminoethylisothiouronium (A.E.T.) and stored autologous bone-marrow. H. M. PYLE (Boston) described the technique for preservation of human bone-marrow with dimethyl sulphoxide. This substance has the unfortunate property of producing a hydrogen-sulphide smell and taste in the recipient but is otherwise harmless, and certainly results in improved uptake of thymidine in vitro.

The physical mechanisms involved in the death of cells at subzero temperatures were described by P. MAZUR (Oak Ridge) and the low-temperature preservation of isolated mitochondria by C. V. LUSENA (Ottawa). D. A. GARDINER (Oak Ridge) discussed the statistical evaluation of experimental variation of conditions for preserving bovine spermatozoa. M. BALDINI (Boston) described the preservation of platelets at low temperatures and emphasised the importance of selecting the most appropriate criteria of successful preservation—in this case the survival-time of platelets after transfusion and the maximum recovery of infused platelets in the recipient's circulation. The problems inherent in the low-temperature preservation of whole organs were discussed by C. E. HUGGINS (Boston), who, taking goldfish as a model, found that a slow increase of ambient glycerin concentration was greatly superior to a rapid increase; and by AUDREY SMITH (London), who showed by means of a very convincing film that dimethyl sulphoxide is better than glycerin in avoiding circulatory side-effects during infusion of the preservative, and that the hamster heart is remarkably tolerant to rapid increase in the ambient concentration of the sulphoxide. The successful recovery of hearts frozen to −10°C in the presence of 12% dimethyl sulphoxide was reported.

1. Barnes, D. W. H., Loutit, J. F. *J. nat. Cancer Inst.* 1955, **15**, 901.
2. Smith, A. U. *Proc. R. Soc. Med.* 1954, **47**, 57.
3. Polge, C., Lovelock, J. E. *Vet. Rec.* 1952, **64**, 396.

In England Now

A Running Commentary by Peripatetic Correspondents

As one who has done more perhaps than any other living person to foster (Aug. 12, p. 367) the use in this country of Superdiagnostex, I was horrified to read in the *Observer* recently of the introduction in America, for the same purpose, of the electronic computer, which only a set of materialistically minded morons would even dream of applying to the Hippocratic art. Still, 1984 gets closer in all senses. Who can say whether the following scene from a London teaching hospital of that future historic year is too far-fetched or not?

The Robot was doing his round. Recently appointed to the consultant staff, the Robot was impassive-faced, steely featured, flashing-eyed, the strong silent type (apart from certain soft whirring noises that betokened internal activity)—in a word, the idol of the nurses' home. Led from bed to bed by the houseman and registrar, the Robot made diagnosis after diagnosis with pettifogging accuracy. Reaching the last bed in the ward, the Robot was assimilating the physical signs (fed in by the registrar) when a scream rang out. It was Evans-the-houseman. Convulsed and shouting, he flung himself on the Robot's flex and pulled the plug out of the wall socket. A blissful silence settled on the ward apart from the soft sobbing of Evans, crumpled in a heap by the X-ray box. "There, there," said Sister. "Working too hard most likely." Plugging in the Robot again, "DO carry on, Sir," she breathed, similing ecstatically up into the Robot's expressionless twin frontal dials.

A houseman I know who works for a neurologist gave a hollow laugh at this point. He says it's a pity his own man is a rather more complicated model. He doesn't seem to have a flex.

* * *

Robinson was a pleasant chap and known to his colleagues and patients as a well-informed and competent practitioner. It was not always so.

I first knew Robinson as a rather new clinical student. Nobody quite understood how he passed his exams since he appeared averse to any form of studying. Even as a clinical student he was rarely seen in the wards and never at a lecture. It was not long before we found ourselves doing midder and there was considerable speculation on Robinson's debut as a midwife. We were on the District together, and the very first evening Robinson was called out. He turned down all offers of help and we waited expectantly for the phone to ring. It was not long, however, before Robinson returned smiling quietly and assuring us that all had gone off perfectly and he had delivered a fine son and heir. He also added that he could not see why so much fuss was made over what was, after all, a perfectly natural process.

There was a slight sense of anticlimax and little interest was shown when Robinson was called a second time. The telephone call came, I remember, during a game of poker. "It's Robinson," someone called. "He sounds worried and is asking for help." I hurried to the telephone. "Hullo, what's the trouble?" I asked and could not help adding, "I thought childbirth was a perfectly natural process." "Natural!" Robinson almost exploded down the telephone. "Natural childbirth is all right, but this one is coming out head first."

* * *

I have been reading this column now for more years than I care to remember (When, Sir, did it first appear ?*) and occasionally the title disturbs me faintly. I have no doubt that at first it was literally correct; but, as a Scot and an occasional correspondent myself, I know that events from my side of the Tartan Curtain are recorded for posterity from time to time. "In Britain Now" might just be acceptable after we became used to it, but the trouble is that it is not comprehensive enough and "In the World Now" will just not do. I am afraid it must be left as it is for it would not be the same with a new title, and yet . . .

* Sept. 23, 1939—ED. L.

Letters to the Editor

INDUSTRY AND PROFESSION

SIR,—In all of the letters of Sept. 2 on this subject there is a note of unease about the relationship between the medical profession and the pharmaceutical industry. It is justified, for the two have been sniping at one another for many years past; each the while having been enfiladed by other interested parties. Some of your readers will know that the recent Kefauver investigation of the American pharmaceutical industry has led to proposals for new legislation aimed at a further, major degree of Governmental restraint of it. They may know also that the American Medical Association has condemned certain crucial elements in these proposals.[1] It is not impossible that similar proposals by Government will be made in this country. Recent actions of the Minister of Health in relation to the industry would certainly not lead one to dismiss the foreboding.

Amid the mutual sniping of industry and profession a minority on both sides forget what is in my view the central feature of the relationship. Most of the major therapeutic advances of the past twenty years have come from the pharmaceutical industry. They were, however, assessed by doctors, and often helped to clinical fruition by them; and if doctors did not prescribe the industry's products (the humdrum as well as the brilliant), the ethical industry would cease to exist—as, indeed, it might if any hard curb were put upon doctors' freedom of prescribing. These are truisms, but worth stating, like "people in glass houses . . .". The basic fact is that the profession could not practise modern medicine without the industry; and that the industry could not exist without the profession. We need one another.

Despite this central truth the petty recriminatory hubbub goes on. The industry, say some doctors, makes excessive profits; it indulges in excessive and irrelevant promotion of its products; it does not have them fully tested before launching them; it goes in for dubious polypharmaceuticals. The industry has its criticisms of the profession too, though I am bound to say it is usually less vocal with them. Doctors, says the industry, will *not* always test new products fully for us (and who else can?); our raison-d'être in a free economy *is* to make profits; if we don't *somehow* tell doctors about our products, they will never prescribe them; and as for polypharmaceuticals—the biggest collection of them can be found in the *National Formulary* (but of the hallowed kind). And so on and so on. A few doctors seem to think the industry is run entirely by subhuman worshippers of the cash nexus; a few of those in industry that all doctors are negativistic, ululating Druids. In each case, of course, the truth is far different; but the glowering continues.

Knowing both industry and profession, I have long regretted one major feature of the gulf between them. The chemists, pharmacologists (and the directors) of the industry, and, on the other hand, physicians, surgeons (and, say, the profession's panjandrums—the medical editors) neither understand nor have any means of thoroughly understanding the work, the thinking, and the aims and problems of the other group. Time and time again I have heard from both sides: "If only I could have access to . . ." And many of your readers must have seen the splendid laboratories and equipment of pharmaceutical firms, and have contrasted them with what often obtains in the non-

1. *J. Amer. med. Ass.* 1961, **177**, 190.

clinical departments of medical schools. Yet, by and large, the schools have men of a calibre that the industry cannot now attract. A double levelling-up seems long overdue.

What then is to be done? I should have thought that, in view of what I have said, it was obvious: some kind of reasonably close and formal cooperation between industry and profession is needed. A limited cooperation there is already. Pharmaceutical firms give a good deal of money to medical institutions and for various research projects; they provide scholarships. In turn, a number of distinguished individual doctors act as consultants to pharmaceutical firms; many clinical trials of new drugs are carried out, and so on. But I envisage a very much wider cooperation than that; and one that would prevent the occasional abuses—by one side or the other—that exist under the present, often unpublicised arrangement.

Also, the cooperation I mean would not be a centrally sponsored and supervised one. The British Medical Association and the Association of the British Pharmaceutical Industry do now consult one another on many matters of mutual interest; but they would probably be the first to agree that an attempt by them to control a full, countrywide linkage of industry and profession would result in stagnation rather than in cooperation, in unwieldy floundering rather than in fruitful understanding. Only Governmental control of the industry would be better calculated to prove less helpful—to the country, as well as to the industry and the profession. No-one can want to see in twenty years a Beeching or a Robens called in to revive a moribund industry. It would obviously be preferable for its youthful and exuberant vigour to be wisely guided into maturity, rather than frustrated into a premature senility.

What form then should cooperation take? Where in the profession are the appropriate repositories of wisdom? For youth? There are twenty-three medical schools in the United Kingdom, and very roughly the same number of large pharmaceutical firms. Would it not be best for each firm to have a formal and acknowledged union with one medical school? Thus assuring to the marriage the virtues of two small, autonomous units, and not the defects of a liaison between amorphous colossi. (The B.M.A. and the A.B.P.I. would, of course, have some grandparental functions to perform.) I do not mean an exclusive and inflexible union between school and firm, but a staunch, friendly, and normally permanent one. The school might be given some of those " excessive " profits, to be used in its own research departments or on any other project it might desire. In return it would provide advice to the firm from its array of professors and lecturers, even from its registrars; it might link some of its own research with that of the firm; it would, by and large, try to give priority (no more) to trials of the firm's new products; it would raise a deprecatory and respected hand in the face of any proposed promotional excesses. It would, I believe, profit a good deal in return—in ways other than financial.

It would be impertinent of me to attempt to discuss the fine details of a union of this type. Those better qualified than myself can do so. But will they? Or will they raise their hands and bemoan the suggestion as bristling with insurmountable difficulties, or as calling for the setting up of various committees to give the idea the prolonged and careful consideration it merits—i.e., to kill it dead. I am aware of some of the difficulties involved, for I have had this concept in my head for a number of years, and have discussed it with various people in both industry and profession.

What, for instance, it will be said, is to happen to the smaller firms? Well, would it not be possible, even desirable, for any one medical school to form an attachment to two or three firms? There are advantages in polygamy—to the husband. Or are there no groups of peripheral hospitals that could give to a smaller firm a service as excellent as that some medical schools might provide for the bigger? And, of course, there will be, " But what is to happen to the integrity of the profession?" I have sufficient faith in it to think its fate would be the same as that of those many firms who by and large are now conscientiously trying to give of their best—both would flourish. But what would a firm's shareholders say when they saw some of its profits being milked away to equip, say, a new pædiatric unit? They would swallow hard at first, but they would soon be applauding the increased flow of valuable new drugs that would, I believe, emerge from an intimate personal understanding of each side by the other on the technical plane. Intimacy alone leads to fecundity.

There are plenty of difficulties, but I do not myself think they are insurmountable. At least a revocable start could be made—in a small way, between a handful of schools and as many firms. Between, say—as a purely alliterative suggestion—Glaxo and Guy's, Boots and Belfast, Lilly and the London. I should be happy if my suggestion were at least considered by responsible men on both sides, so long as they remembered, first, that industry and profession do need one another, and second, what the alternative might in due course be.

Perhaps I should end by saying that, as well as being a doctor, I have had some years of experience in the industry. At present I advise one ethical pharmaceutical firm, but I am not dependent upon it for the major part of my livelihood; nor do I speak for it. I write this only so that I may not be accused of grinding any axes—for the industry or for the profession—and to make it clear that I have some experience of both sides of the matter. I think that the time left for action is short. So too, by the same token, is the time for sniping, glowering, and committeemanship. The wind of change is not going to pause at the hems of any latter-day Canutes.

Little Missenden, Bucks. S. BRADSHAW.

SIR,—Having read your editorial of Aug. 19 and the subsequent correspondence, I am forced to the conclusion that much of the misunderstanding which exists between the industry and the profession arises from the fact that there is an apparent lack of knowledge within the profession of elementary business procedure, particularly as it pertains to advertising. For example, every advertisement contains an element of information and an element of persuasion, and there is no such thing as " straightforward information ". Taplin [1] puts it even more bluntly when he says " that anyone who suggests that advertising can in practice be a matter of information only is talking nonsense ".

To condemn repetitive advertising is to disapprove of a sound advertising technique, and to criticise the industry for employing advertising experts, or to suggest that advertising can sell anything, is to be ridiculous, for while many educated persons do consider themselves to be knowledgeable in this field, industry has long since learned to leave the subject in the hands of specialists.

1. Taplin, W. A New Approach to Advertising. London, 1960.

The widely held view that the drug industry is extravagant in its expenditure on advertising is also probably false. If we take other industries selling consumer goods as our controls, where an expenditure of 10% of sales revenue is considered to be average, we find that the drug industry spent only £2·15 millions on direct mail and samples,[2] and a further £2 millions (estimated) in the medical Press, making a total of £4·15 millions, or only 8·3% of their sales revenue. I have purposely omitted to include the representative, as he is comparable to the salesman in industry and as such cannot be assessed as true advertising expenditure. The figure of £4·15 millions spent by the drug industry is less than the £7·6 millions [3] spent by Unilever on advertising in 1957, and the £7·8 millions [4] spent on promoting food and drink on television in the three-month period January to March, 1960.

While it would be foolish to suppose that all is well in the field of medical advertising, it should also be borne in mind that by demanding the right to prescribe freely for his patients the doctor creates the atmosphere in which medical promotion can flourish, and to suppress it forcibly is to jeopardise his freedom of prescribing. It is pertinent to ask how much promoting exists in the Russian medical State salaried service.

Surely it is time our profession met the drug industry and discussed the problem in a more businesslike fashion.

Hawick, Scotland. RODERICK R. HAMILTON.

SIR,—The correspondence in the issue of Sept. 2 was of much interest.

Dr. Binns emphasises the medical profession's responsibility in this matter, and he well crystallised the situation in his last sentence: " It seems to me that in every country the profession gets the industry it deserves."

I cannot, however, admit to having done a disservice to the pharmaceutical industry and to the profession, as suggested by Dr. Gorringe. Untoward pressures do arise during the conduct of clinical trials, as can be witnessed by those involved in them. This, in fact, is an inevitable component of our competitive society. Preclinical toxicity testing, though admittedly not the last word in precluding risks to human subjects, is by no means such a standardised and routine procedure as Dr. Gorringe would have us believe.

The point I was trying to make was that it behoves *both* physicians and industry to resist untoward pressures for the sake of the recipient of the results of therapeutic research—the patient.

YOUR CORRESPONDENT OF AUG. 19.

FARMER'S LUNG

SIR,—The cause of this condition, discussed in your annotation of Sept. 2, has not yet been properly defined. In recent years, awareness of the condition is increasing, and it is more common than was originally thought. Diagnosis, however, is still difficult in the milder cases, and one of the criteria for diagnosis used to be a characteristic X-ray picture. In order to produce such a picture, however, structural changes must have occurred in the lung.

Farmer's lung is due to the inhalation of vegetable dusts, and in this, as well as in clinical appearances, it has much in common with, for example, pulmonary aspergillosis, bagassosis, broken wind of horses, and paprika-splitters lung. In farmer's lung, however, the symptoms often arise some time—two to twelve hours—after exposure. This is a significant fact, and serves to differentiate the disease from asthma due to allergy to the particles of vegetable material. In asthma, the symptoms arise immediately on exposure. In this respect, it is a self-limiting illness, for the worker straightway associates his discomfort with its cause, and promptly removes himself from the dust. On the other hand, the delay in onset of the symptoms of farmer's lung causes the worker to expose himself to the dust for longer periods. Since a large measure of recovery may occur during the night, and since he does not readily associate his illness with the hay dust, the farmer returns to work, and further exposure, next day.

This delay in onset of symptoms may be a clue to the cause of the disease. Hunter,[1] discussing the ætiology of bagassosis, remarks that it is probable that bronchioles fill with vegetable dust which swells, blocks, and causes small areas of collapse. When these areas are infected, bronchiolitis, or bronchopneumonia, may result. In farmer's lung, it is this blockage of the finer branches of the respiratory tree which causes the symptoms, the duration of which seems to depend upon how soon the branches can be cleared by coughing. In small, short exposures, this is a matter of a few hours, but in more severe exposures, and particularly in the presence of intercurrent infection, clearing may take much longer. Of cases reported recently by Hutt [2] the two worst were those who had had influenza three months previously.

In mouldy hay, aspergilli appear to be the commonest species found, and indeed their spores are often liberated from bales in overwhelming numbers. Many of these are caught in old dry cobwebs in the corners of hay lofts, and the smoke-like dust shaken from these cobwebs on to slopes of Sabouraud's medium yielded colonies which were morphologically indistinguishable from *Aspergillus fumigatus*.

The size of the spores—about three microns—would seem to permit their inhalation right into the alveolus. They germinate at 37°C, in the presence of moisture, protein, and sugar, and these are all to be found in the bronchiolar secretions. Indeed, irritation of the respiratory tract, for any reason, results in an increase in these secretions.

As a result of recent investigations by Dickie and Rankin [3] and Seal et al.[4] it is becoming accepted that farmer's lung is capable of causing disability, in the form of fibrosis of the lung. This will no doubt denote it as a candidate for inclusion in the prescribed list of industrial diseases, and also as a contributing factor in the ætiology of chronic bronchitis. The essential cause is blockage of the bronchioles by vegetable matter—in farmers, most probably by germination of the spores of aspergilli—and the pulmonary fibrosis which occurs in severe cases is possibly determined by pre-existing infection in the lung.

Barnard Castle. K. H. PICKWORTH.

NURSING CURRICULUM

SIR,—In your issue of Sept. 2 Miss M. M. C. Louden, F.R.C.S., appeals for additional examiners from the medical profession and suggests that some of the critics of previous examination papers might apply for an examinership and, if appointed, change their views.

We are among those who have criticised [5] a final examination paper for nurses, and we now reiterate our contention that, since the examiner " calls the tune ", the prospective nurse is forced to learn much theoretical knowledge of greater value to the doctor than the nurse. This tends to draw teaching away from strictly nursing matters to the detriment of the nursing profession. To

2. Committee of Public Accounts, 3rd report, 1960–61, July, 1961. H.M. Stationery Office.
3. Harris, R., Seldon, A. Advertising in a Free Society. London, 1959.
4. Statistical Review of Independent Television Advertising, 1960, vol. 5, no. 2.

1. Hunter, D. The Diseases of Occupations; p. 959. London, 1957.
2. Hutt, C. A. *Brit. med. J.* June 3, 1961, p. 1611.
3. Dickie, H. A., Rankin, J. *J. Amer. med. Ass.* 1958, **167**, 1069.
4. Seal, R. M. E. Association of Clinical Pathologists, April, 1960. (See *J. clin. Path.* 1960, **13**, 271.)
5. *Lancet*, 1959, ii, 125, 411.

maintain interest and ensure an attractive presentation, a lecturer is well advised to introduce matters of purely medical or scientific interest, but it is not reasonable to *examine* the student upon these matters.

Nevertheless, we accept Miss Louden's invitation to apply to become examiners, assuming that we could conscientiously discharge our duties according to our convictions.

Department of Pathology,
Whipps Cross Hospital,
London, E.11.

W. W. WALTHER
C. RAEBURN.

STEAM STERILISATION

SIR,—Dr. Fallon (Sept. 9) finds that even downward-displacement steam sterilisers tend to damage nylon bags. Nylon bags are made in several thicknesses: a foil of gauge C 0·002 in. thick is the most effective. It is possible that Dr. Fallon used a foil of greater thickness than 0·002 in.

The seal around the aluminium tube is quite effective, as described in my letter of July 8.

The steam pressure in a downward-displacement steriliser may exceed 30 lb. per square inch. The high-vacuum steam steriliser seldom exceeds a steam pressure of 25 lb. per square inch in the chamber.

If a small nylon pack is made up, sealed, with a few swabs inside, it is quite easy to place it in an all-glass anaerobic jar and exhaust the contained air with an Edwards high-vacuum pump. What happens to the nylon bag can be watched at all stages. A glass door to the high-vacuum steam steriliser would also enable one to see what was going on inside.

After the tests in the exhausted anaerobic jar, the same trial packet may be placed in the high-vacuum steam steriliser and treated with a routine load, and subsequently examined for flaws, lack of sterility, &c.

St. Margaret's Hospital,
Epping.

FRANK MARSH.

FORMATION OF CALCULI

SIR,—In their interesting paper (Aug. 26) on the formation of calcium-oxalate calculi, Dr. Hodgkinson and his colleagues again draw attention to the interplay of the two hydrates of calcium oxalate in stone formation. According to them, calculi with large crystals develop by crystallisation and therefore require supersaturation (contributed to by hypercalcinuria), striated calculi develop by adsorption in a calcifiable matrix. Although they make it clear that striated calculi develop from only the monohydrate of calcium oxalate, they suggest that large crystals of this mineral are also common. This has not been my experience—large monohydrate crystals, though they do occur, are of great rarity.

The relationship between the two hydrates in urinary tract deposits is an intriguing puzzle. Under all normal circumstances of temperature and pressure calcium oxalate monohydrate is the stable crystalline form and the dihydrate is unstable. Why then do calculi composed of calcium oxalate dihydrate—and "envelope" crystalluria—occur at all? A clue lies in the peculiar behaviour of the monohydrate when it crystallises out of urine. Instead of the pointed twinned crystals which develop in aqueous solutions, rounded deposits occur which resemble dumbbells or biscuits according to their orientation with respect to the observer. Similar deposits can be produced by the laboratory crystallisation of calcium oxalate in aqueous gelatin solutions.[1] Morse [2] has shown these rounded deposits to be microcrystalline aggregates and to be the first step in spherulite formation which is responsible for radial striation. The basic process is, however, still crystallisation, and supersaturation is as necessary for it as for any other form of crystallisation. The extreme ease with which spherulites can be grown from a large variety of minerals in many gelatinous media [2] precludes any vital relationship between matrix and crystals.

All the evidence which indicates importance of a "calcifiable matrix" is concerned with calcium phosphate calculi.[3] It is in these calculi that an acid mucopolysaccharide matrix has been identified [4]; the mineral is apatite—the mineral of bone salt and all pathological calcifications—and moreover calcium phosphate is the only mineral forming fine-grained calculi in which radial striation is not found.

Bury.

J. A. CARR.

MANAGEMENT OF THIRD-STAGE COMPLICATIONS IN DOMICILIARY OBSTETRICS

SIR,—With regard to the correspondence arising from our article of July 15, we should like to emphasise that in reviewing current practice we were struck by the constant similarity of management of third-stage complications regardless of the differing circumstances under which flying-squads operate. We put forward the view that in certain clearly defined circumstances another concept of management was feasible; this was substantiated by our results.

We agree that domiciliary anæsthesia is safe providing there is available an expert obstetric anæsthetist with all his apparatus. In our case, we consider anæsthesia to be safer in hospital. At the present time, the County of London is served by fourteen flying-squads each covering approximately two metropolitan boroughs. Twelve do not have an anæsthetist in the team; in the two that do he is not a consultant.

With regard to the emotional upset of removing patients to hospital, one can say that all is well where obstetric matters go well. When dramatic complications occur, it is our experience that the relatives (and the patient if able to express her views) are only too pleased for hospital care; it is only for 24–48 hours. Furthermore, it relieves the overworked midwife of the exacting surveillance required for the initial 24 hours' aftercare of these patients.

St. James' Hospital,
Balham, London, S.W.12.

A. C. FRASER
E. P. W. TATFORD.

SIR,—We think that Dr. Fraser and Dr. Tatford have been unfairly and unnecessarily criticised for their fresh ideas on the function of the obstetric flying-squad in the management of third-stage complications in domiciliary obstetrics. This country is divided into those areas with and those without a flying-squad. In the latter the patient is often put into an ambulance whatever her condition and sent to hospital. In the former, the flying-squad often completes all treatment in the home. Dr. Fraser and Dr. Tatford have suggested a sane and commonsense compromise between these two extremes. The patient is seen in her home, is resuscitated, and then, if necessary, taken to hospital under expert supervision for any operative procedure.

No-one will deny that the treatment of a third-stage complication in a hospital delivery is easier and safer than in domiciliary practice. The presence of an expert anæsthetist with complete apparatus, electric suction machine, and a tilting delivery bed is surely safer than open ether or chloroform in a private dwelling as suggested by Dr. Staddon (Sept. 2). Consequently we feel that the idea under discussion combines expert resuscita-

1. Carr, J. A. Pathology of the Formation of Calculi. Moynihan prize essay, 1952.
2. Morse, H. W., Donnay, J. H. D. *Amer. Min.* 1936, **27**, 391.
3. Carr, J. A. M.D. thesis, University of Durham, 1957.
4. Howard, J. E., Carey, R. A., Rubin, P. S., Lewin, M. D. *Trans. Ass. Amer. Phycns*, 1949, **62**, 264.

tion at the scene of the possible catastrophe with the safety of hospital surgery and anæsthesia, and is to be commended.

There will be general agreement with Dr. Fraser and Dr. Tatford that many seriously ill cases would have been prevented by eliminating those with specific contraindications to domiciliary confinement and by the general practitioner giving ergometrine intravenously, or mixed with hyaluronidase intramuscularly, preferably after the birth of the fœtal head.

We feel that doctors should be taught the Brandt-Andrews technique so that there will be fewer retained placentas and less blood-loss. We should like to add that any general practitioner undertaking domiciliary midwifery should, in addition to taking blood from the mother during pregnancy for blood-grouping and hæmoglobin estimation, have at hand for the confinement at least two bottles of plasma or plasma substitute, a transfusion giving set, and the training and ability to use them when indicated.

N. KIMBELL
R. E. LODER.

Peterborough.

MEDICINE AND HISTORY

SIR,—The remarks of Dr. Todd (Aug. 26) on the state of medicine in the first decades of this century recall to my mind that in August, 1914, attached to a cavalry regiment supposedly destined for service in the tropics, I found the medical equipment to include a vast supply of bottles containing ipecacuanha tablets for the treatment of amœbic dysentery; but the labels firmly indicated that the contents were " de-emetinised ".

Wolverhampton. S. C. DYKE.

α-HYDROXYBUTYRIC DEHYDROGENASE IN THE DETECTION OF MYOCARDIAL INFARCTION

SIR,—I was most interested in the letter by Dr. Konttinen (Sept. 2).

I should like to point out, however, that the method of H.B.D. determination he used and given in the paper by Elliott and Wilkinson,[1] is that which I developed, and later supplied to Dr. Elliott when he succeeded me in the Department of Chemical Pathology at Westminster Hospital. A full account of this method and temperature correction data are included in thesis material which I have submitted for the M.D. degree of the University of London.

This thesis also describes the differentiation of serum-lactic-dehydrogenase (L.D.) activity from H.B.D. activity (an outline of this has already been published [2]), and records my original observations on the L.D.: H.B.D. ratios of normal and pathological sera and H.B.D. activities.

Department of Pathology,
Kingston Hospital,
Surrey. S. B. ROSALKI.

VACUUM EXTRACTION IN OBSTETRICS

SIR,—Your leading article of July 22 prompts me to write to you about some of the lesions seen in infants subjected to vacuum extraction. It seems that most of the published work on this subject relating to the infant has been mainly confined to infant mortality.

A preliminary study of 166 infants subjected to vacuum extraction in the Kandang Kerbau Hospital in Singapore revealed some lesions which have probably not been described. These include:

(1) Large cephalhæmatomas which transcend suture lines, and may be due to ripping up of the pericranium and its processes in between individual skull bones. Such large hæmatomas often result in anæmia and severe jaundice and in one patient a blood-transfusion had to be given.

(2) Radiological evidence of " erosions " in the skull bones, especially the parietals, were seen in most of the infants with these large cephalhæmatomas.

(3) The presence of air crepitations in the scalp with severe abrasions, and in one case the possibility of air in the extradural or subdural space underlying the extractor.

Infants with these severe lesions often show some neurological signs, such as generalised stiffness, poor sucking reflex, or fits. These infants are being carefully followed up to assess any physical or mental sequelæ.

My purpose is to draw attention to the need for detailed studies of the morbid effects of the vacuum extractor in infants, and for closer cooperation between obstetricians and pædiatricians in such studies, as you have pointed out in your leading article.

A full report of our findings will be published in the near future.[3]

Kandang Kerbau Hospital,
Singapore. WONG HOCK BOON.

TYPE-21 ADENOVIRUS INFECTION

SIR,—So far, adenoviruses of types 3, 4, 7, and 14 have been found associated with outbreaks of respiratory disease. In the Netherlands in 1960 and 1961, virus strains of type 21 were often recovered from patients with acute respiratory illnesses. Type 21 was originally isolated from the conjunctiva of a one-year-old child in Saudi Arabia [4]; we do not know of its isolation being reported elsewhere.

A systematic survey of acute respiratory disease was made at an army recruit-training centre. Paired acute-phase and convalescent-phase sera and throat swabs were collected from patients admitted to sick-quarters with acute respiratory illnesses. Between June, 1960, and January, 1961, 283 pairs of sera were tested; 132 were found to have rising titres of complement-fixing antibodies against adenovirus. In 101 of the 132 serologically positive cases throat swabs were tested in HeLa-cell cultures; 67 swabs yielded adenoviruses. Adenovirus strains were typed by neutralisation tests with specific rabbit sera. The 67 strains isolated were found to be type 21. Throat swabs of 4 patients from whom type-21 adenoviruses were recovered, were retested in another laboratory (at St. Elisabeth Hospital, Tilburg) where no strains of type-21 had been reported. These specimens gave a positive result again in the second attempt at isolation.

Rabbits were immunised with two representative strains of type-21 isolated in this laboratory, and with the prototype strain of type-21 (kindly supplied by Dr. S. D. Bell). The rabbit antisera showed reciprocal cross-neutralisation against these viruses; but the neutralisation titres against the new strains were always higher (2 to 8 times) than those against the prototype strain. The two representative strains from this laboratory agglutinated erythrocytes of the rhesus monkey to a high titre, but failed to agglutinate human " O " and rat erythrocytes.[5] This pattern of hæmagglutination is similar to that of the prototype strain of type 21.[4] Hæmagglutination-inhibition tests showed reciprocal cross-reactions between the two new strains and prototype-21 virus.

Paired sera of 12 patients, from whom type-21 adenoviruses were isolated, were examined for neutralising antibodies against a type-21 strain recovered in this laboratory. There was a fourfold or greater rise in titre in 11 pairs. None of 12 patients infected with type 7 exhibited a significant increase in neutralising antibodies against the new strain.

Between February, 1958, and May, 1960, almost exclusively type-7 adenoviruses were found in military populations in this country. No essential difference in clinical features in recruits infected with either type 21 or type 7 was apparent. Both these types appeared to be associated with the syndrome of febrile catarrh.[6]

1. Elliott, B. A., Wilkinson, J. H. *Lancet*, 1961, i, 698.
2. Rosalki, S. B., Wilkinson, J. H. *Nature, Lond.* 1960, **188**, 1110.
3. *J. Singapore Pæd. Soc.* (in the press).
4. Bell, S. D., Jr., Rota, T. R., McComb, D. E. *Amer. J. trop. Med.* 1960, **9**, 523.
5. Rosen, L. *Amer. J. Hyg.* 1960, **71**, 120.
6. Stuart-Harris, C. H. Influenza and Other Virus Infections of the Respiratory Tract; Chap. 7. London, 1953.

Type-21 virus strains were also isolated from 6 children under three years of age admitted to hospital in 1961. 5 children had bronchopneumonia, 1 bronchitis. Serum specimens were collected in the acute phase of illness and in the convalescent period. The titre of complement-fixing antibodies against adenovirus rose significantly. Adenoviruses were recovered from the throat swab of 5 patients, and from the stool of 1. The strains were found to be of type 21.

Department of Hygiene, Roman Catholic University, Nijmegen, The Netherlands. J. VAN DER VEEN J. H. DIJKMAN.

HELLENOMANIA-HELLENOPHOBIA

SIR,—Hurrah for Dr. Jackson! The next logical step is for *Lancet* and a few other journals around the world to devote a couple of paragraphs in each issue to new medical terminology, listing various possible terms and indicating which is best and why. In time, perhaps we might even abolish some of the more fearsome and repulsive terms which have become popular.

Surely the English language is sufficiently well established that we may assume that it is here to stay: why should we quibble about whether the various parts of a word derive from Greek, Latin, or Sanskrit? They derive from *English* words and syllables which, while they may, buried in antiquity, have roots in other languages, have long been incorporated into our own language. Try to tell a woman that she should not wear Australian wool sweaters over Egyptian cotton dresses over Italian silk underwear, and she will answer that providing the over-all effect is pleasing and the meaning is clear, derivations do not matter a whit! So it is with philology.

Toronto. H. CLARK BALMER.

SIR,—Dr. Jackson's entertaining and pungent article of Sept. 2 provides some delightful reading even if he tantalises the memory by failing to print the limerick based on dysdiadochokinesis. But has he fallen down, I wonder, on p. 543, when he writes " . . . their content will be not *hemos* but *blut* or *sang* . . ."? According to my information classical Greek had the word αἷμα, retained unaltered in present-day Greek. From where then does *hemos* come—or is the error mine?

County Hall, Lewes. F. LANGFORD.

ACUTE POISONING

SIR,—With reference to your annotation of Aug. 5, readers may be interested to know that poison control centres have been existing in Canada since 1957 and in the U.S.A. since 1953.

There are, in all, 191 Canadian centres, each with the same basic structure. At least one is situated in every major centre of population and its services are readily available to outlying districts. The centres are equipped with an index cabinet giving information on the toxic constituents of all commonly used household chemicals and patent medicines, together with suggested treatment of poisoning. They provide a 24-hour service of information and advice to physicians, and to the lay public. In addition, they are equipped to treat all types of poisoning. All treated cases and telephone inquiries are reported to a central pool kept by the Food and Drug Directorate of the Department of Public Health in Ottawa. A physician wishing to make a statistical study of some aspect of poisoning in Canada may request information from this pool.

From May, 1957, to December, 1959, 10,982 treated cases were reported from the poison control centres across Canada. Among these there were 23 deaths (17 children and 6 adults) due to accidental poisoning. It is estimated that a further 10,000 cases were reported in 1960.

Winnipeg, Manitoba. VERA GLLMAN Director, Poison Control Centre, Children's Hospital.

HEAT STABILITY OF ANTINUCLEAR FACTOR IN SYSTEMIC LUPUS ERYTHEMATOSUS

SIR,—Serum antinuclear factor(s) (A.N.F.) has been demonstrated by Coons' immunofluorescent technique [1] in various conditions besides systemic lupus erythematosus (S.L.E.), in which it was first described.[2 3]

The possibility of distinguishing between the reactions obtained in patients with S.L.E. and in those with other diseases has been studied; preliminary results indicate a qualitative difference based on heat-stability.

Sera from 48 patients were examined. All of them gave a positive antinuclear-factor reaction in the fluorescent test. The 48 patients included 23 with S.L.E., all of whom satisfied the criteria submitted by Bywaters and Ansell to the M.R.C. Collagen Panel, 1952 (appendix [4]) and 25 other patients, mainly with rheumatoid disease.

The sera were diluted 1 in 10 with 0·16 *M* sodium-chloride solution and heated at 65°C for thirty minutes. The A.N.F. test was carried out as previously described [4] but using calf thyroid instead of human thyroid as substrate. Pairs of sections were treated with heated and unheated serum—both diluted 1 in 10—and stained with fluorescein-labelled anti-human globulin conjugate. The nuclear immunofluorescence obtained with heated and unheated sera was compared.

It was found that heating did not impair the brightness of the staining obtained with many of the sera, or brought about only a partial reduction. However, with some sera the effect of heating was to abolish the reaction completely (tables I and II). The maximum intensity of fluorescence is recorded in tables I and II as +++. Although based on a subjective impression, this system has been found to give as good reproducibility in blind tests as titration, in which there is considerable difficulty in establishing the end-point of specific fluorescence.

TABLE I—EFFECT OF HEAT ON THE A.N.F. REACTION: SERA REMAINING POSITIVE AFTER HEATING

Diagnosis	No. of cases	Reaction before heating				
		+++	+++	++	++	+
		Reaction after heating				
		+++	++	++	+	+
S.L.E.	23	13	3	4	3	
Possible S.L.E.	3			3		
Rheumatoid arthritis (R.A.)	2		1		1	
R.A. + arteritis	3			3		
R.A. + Sjögren's syndrome	2	1			1	
R.A. + L.E. cells	1			1		
Dermatomyositis	1					1
? Sjögren's syndrome ? Raynaud's phenomenon	1			1		
Totals	36	14	4	12	5	1

TABLE II—SERA BECOMING NEGATIVE AFTER HEATING

Diagnosis	No. of cases	Reaction before heating	
		++	+
R.A.	2	2	
R.A. + arteritis	4	3	1
R.A. + Sjögren's syndrome	1	1	
R.A. + amyloid disease	1		1
Still's disease	1	1	
Rheumatic fever (? Jaccoud's syndrome)	1	1	
Sjögren's syndrome + discoid L.E.	1	1	
Scleroderma	1	1	
Totals	12	10	2

The tables show that none of the sera from cases of S.L.E. became negative on heating. Although many of these sera showed the brightest staining in the series before heating, they include 7 which were, on subjective assessment, no stronger in their original reaction than 10 of the sera which did become negative on heating. This suggests that heating does not merely abolish positivity in weaker sera, but has a specific discriminating effect.

1. Coons, A. H., Kaplan, M.H. *J. exp. Med.* 1950, **91**, 1.
2. Friou, G. J., Finch, S. C., Detre, K. D. *Fed. Proc.* 1957, **16**, 413.
3. Holborow, E. J., Weir, D. M., Johnson, G. D. *Brit. med. J.* 1957, ii, 732.
4. Weir, D. M., Holborow, E. J., Johnson, G. D. *ibid.* 1961, i, 933.

The possibility that the A.N.F. found in some patients with conditions other than S.L.E. is a heat-labile macroglobulin, and that the factors occurring in S.L.E. include a heat-stable 7S globulin is now being investigated. Goodman et al.[5] have shown that, in S.L.E., antinuclear factors appear in both 7S and 19S γ-globulin fractions.

On the basis of the results described it appears that the demonstration in a patient's serum of antinuclear factor which is inactivated by heating at 65°C is against a diagnosis of S.L.E.

We are grateful to Prof. E. G. L. Bywaters and Dr. W. Hijmans for providing sera from their patients and clinical assessments.

M.R.C. Rheumatism Research Unit,
Canadian Red Cross Memorial Hospital,
Taplow, Maidenhead, Berkshire.

G. D. JOHNSON
E. J. HOLBOROW.

THE FIBERSCOPE

SIR,—I have read with interest the article by Dr. Hirschowitz.[6]

"It may be stated unequivocally that the fiberscope has already reached the stage where it should replace the conventional gastroscope. We would no longer consider using the old instrument" . . . "The conventional gastroscope has become obsolete on all counts."

I have personally used the Hirschowitz fiberscope and find it lacking in three important respects: (1) inability to obtain and maintain an accurate focus; (2) impossibility of proper orientation; (3) unavailability of biopsy. To my mind these three deficiencies make the Hirschowitz fiberscope definitely less useful than many of the conventional gastroscopes.

In principle I believe the fiberscope has great possibilities, but at the present time I believe that it is much less useful than Dr. Hirschowitz claims. Further experience with it may modify my opinion.

Department of Surgery,
Massachusetts General Hospital,
Boston, Massachusetts, U.S.A.

EDWARD B. BENEDICT.

EXTREME HYPERGLYCÆMIA WITHOUT KETOSIS

SIR,—Very high blood-sugar levels may be found in diabetes mellitus. Meyer and Salt's [7] patient had the highest ever recorded, even after receiving 600 units of soluble insulin—2100 mg. per 100 ml. Lawrence [8] described an elderly diabetic in coma whose blood-sugar level reached 2060 mg. per 100 ml.; 40 units of insulin had been given before this estimation.

A Jamaican, aged 34, was admitted to hospital with a two-week history of weakness, anorexia, thirst, and loss of weight. He was drowsy, severely dehydrated, and wasted; his breathing was acidotic. His temperature was 95° F, pulse-rate 100 per min., and respiration-rate 24 per min. There were no abnormal signs on systemic examination. The urine gave a strongly positive reaction for glucose; and the blood-sugar level was 1996 mg. per 100 ml. But ketones were absent from urine and serum (qualitative test). Treatment was started with soluble insulin (230 units in four hours), intravenous isotonic saline, *M*/6 sodium lactate solution, and crystalline penicillin; but the patient died in four hours. Necropsy findings were bronchopneumonia due to acute tracheobronchitis, and diabetes mellitus. The pleural fluid (volume 50 ml.) contained 663 mg. glucose per 100 ml.; but ketones were absent.

Hyperglycæmia per se does not lead to death except as a result of changes brought about in renal function. Why diabetic ketosis is so unpredictable has not been resolved. The onset will depend upon the degree of metabolic disturbance, which can be judged by the blood-sugar level. In this case its absence cannot easily be explained.

London, S.E.18. M. O. P. IYENGAR.

5. Goodman, H. C., Fahey, J. L., Malmgren, R. A., Brecher, G. *Lancet*, 1959, ii, 382.
6. Hirschowitz, B. I. *Lancet*, 1961, i, 1074.
7. Meyer, P. C., Salt, H. B. *Brit. med. J.* 1951, i, 171.
8. Lawrence, R. D. *ibid.* 1934, i, 377.

ICE ARREST OF THE HEART

SIR,—Mr. Ross (Aug. 5) reported the successful use of saline ice crystals applied to the heart to produce arrest during open heart surgery. It must be pointed out that when saline freezes the concentration of salt in the crystals is significantly less than in the unfrozen supernate; similarly, after decanting the supernate and applying the crystals to the heart, that part which melts first has a lower concentration of salt than have the still frozen crystals. These two sequences do not negate each other, however. Since we are striving for an ever less toxic method to cause arrest, it would be helpful to achieve a final saline concentration closer to the physiological one.

Medical School,
University of Pennsylvania. RICHARD ARKLESS.

INTRAVENOUS ALBUMIN IN THE TREATMENT OF DIURETIC-RESISTANT ASCITES IN PORTAL CIRRHOSIS

SIR,—Infusion of protein solutions to patients with cirrhosis of the liver and ascites provides the opportunity for studying the relationships between changing hydrostatic pressure, protein concentration, and colloid osmotic pressure of plasma and ascitic fluid. It might be anticipated that such observations would help to elucidate the factors governing ascites formation and reabsorption. The literature on this subject is considerable, but the contribution of Dr. Losowsky and Dr. Atkinson reported recently in your columns (Aug. 19) is extremely valuable, being the first attempt to compare the concurrent changes in hydrostatic and colloid osmotic pressures. The proportion of their patients who responded to therapy is similar to that of other series, and so their group is probably a fair sample of this type of patient.

It is very satisfactory that inspection of data on portal pressure has enabled them to show that patients who respond to albumin infusions have, before therapy, a lower mean pressure than those who do not respond. A higher intracapillary hydrostatic pressure is presumably related to a greater leakage of protein and fluid, and therefore a greater load on the lymphatic system.

Why some patients should respond to albumin infusions and some should not has puzzled most investigators, and study of Losowsky and Atkinson's data and explanation unfortunately fails to clear the confusion. They have shown in fig. 4 that whereas in those patients where treatment was unsuccessful there were parallel rises in intrasplenic pressure and plasma colloid osmotic pressure, in those in whom treatment was successful intrasplenic pressure did not rise and in some cases fell considerably, final values being found to lie on the right of a line they have produced from previous observations.[1] They conclude from this that " . . . this rise in splanchnic capillary pressure may more than counterbalance any rise in plasma colloid osmotic pressure resulting from the infusions, . . .". It is, however, surprising that any form of therapy designed to expand blood-volume without greatly increasing cardiac output can result in a fall in any venous pressure, and indeed Starling demonstrated that rapid saline infusions in dogs will raise both systemic and portal venous pressures concomitant with an expansion in blood-volume.[2] The hæmatocrit measurements of Losowsky and Atkinson suggest an average expansion of total blood-volume of 12·4% and 17·9% in the

1. Atkinson, M., Losowsky, M. S. *Quart. J. Med.* 1961, **30**, 153.
2. Starling, E. H. *J. Physiol.* 1895–6, **19**, 312.

successful and unsuccessful groups respectively, assuming no change in red-cell mass. In spite of this increase of 12·4% in the total blood-volume of patients sustaining a diuresis, the mean intrasplenic pressure of the four patients concerned was 33·7 cm. water before and 33·2 cm. water following infusions. Under the conditions of study one may ask exactly what pressure has been measured. The values obtained must be a combination of three factors: (*a*) the pressure which blood in the portal vein exerts outwards against its wall (portal venous pressure); (*b*) the hydrostatic pressure of the ascites lying above the zero point of measurement; and (*c*) the tension exerted by the abdominal musculature.

Losowsky and Atkinson have considered the possibility that a rise in ascitic fluid hydrostatic pressure might be responsible for the rise in portal pressure in their unsuccessful group, but they have not entertained the possibility that elimination of ascites and hence a drop in ascitic fluid pressure might produce a fall in the pressure recorded from an intrasplenic needle. The two patients from their successful group in whom such measurements of ascitic fluid pressure were recorded showed falls from 16 to 7 cm. water and 16 to 10 cm. water following the diuresis. The spleen is a relatively soft organ, likely to transmit external pressure, and I would suggest that if paracentesis had been performed on their patients 7b, 8, 9, and 10 at the completion of the course of infusions, a drop in intrasplenic pressure would have been observed similar to that recorded in patients 1–7a.

My conclusions from this data would therefore be that the differences in response of intrasplenic pressure between the two groups are the result rather than the cause of the diuresis. Whilst it is generally believed that the major factors in the development of cirrhotic ascites are portal pressure and plasma-colloid osmotic pressure, the creation of a formula based on the dividing line of Losowsky and Atkinson masks the contributions which other influences such as capillary permeability and the capacity of the lymphatic system make to this complicated problem.

Department of Experimental Pathology
The Medical School,
Birmingham.

P. W. DYKES.

SIR,—I read with interest the article by Dr. Losowsky and Dr. Atkinson (Aug. 19). I note that 4 patients out of 10 in their series died of hepatic failure about four to five weeks after albumin therapy. I would like to ask the authors:

(1) Did these 4 patients have histories of hepatic coma or precoma and, if so, did they have more such episodes than the others?

(2) What was the clinical course of these 4 patients in the five weeks before death? Did rapidly progessing liver-failure develop after albumin therapy? It would be most interesting to know whether the influence of albumin therapy on the course of hepatic failure in these 4 patients differed from that in the others.

50 g. of albumin a day given intravenously, in addition to the usual dietary proteins, can be a great burden on an already failing liver. It is clear that ammonia intoxication can occur as a result. Should arterial-blood ammonia not be estimated and the result considered before starting such therapy?

St. Ann's General Hospital,
London, N.15.

SIRAJ-UD-DIN AHMED.

*** This letter has been shown to Dr. Atkinson and Dr. Losowsky, whose reply follows.—ED. L.

SIR,—We would disagree with Dr. Ahmed's suggestion that albumin infusions are liable to precipitate liver-failure. Our patients had advanced liver-disease, and this accounted for the high long-term mortality.

The incidence of episodes of hepatic coma or precoma before treatment was not significantly higher in the patients who died in liver-failure after treatment than in those who survived; such episodes had been recorded in 3 of the 5 patients who subsequently died in liver-failure four to eighteen weeks after albumin therapy, and in 2 of the 5 survivors.

On no occasion did the albumin infusions appear to accelerate hepatic failure, though in 2 patients the rate at which ascites accumulated was temporarily increased by albumin therapy. More frequent paracenteses were necessary, which might have favoured the onset of hepatic coma.

Blood-ammonia levels were not estimated routinely in our patients, but we encountered no clinical or electroencephalographic evidence to suggest that these rose after the albumin infusions.

Our overall impression was that in a group of patients with severe liver-disease liable to develop jaundice and hepatic coma, albumin infusions, whatever their effect on ascites formation, represent a safer method of treatment than the others now available.

Department of Medicine,
The General Infirmary,
Leeds.

M. ATKINSON
M. S. LOSOWSKY.

STEROID THERAPY IN JAUNDICE

SIR,—We are particularly concerned with the investigation of hæmolytic disease in the newborn in this hospital. Some of the suggestions in Dr. Marsh's letter of Sept. 9 might bear closer examination, but we wish to emphasise that these suggestions are not included in our present practice. However strong the theoretical reasons, we would hesitate to give a preparation such as 6-mercaptopurine to any pregnant woman, whatever effect this might have on hæmolytic disease.

St. Margaret's Hospital,
Epping.

I. M. TUCK
P. D. ROBERTS.

SIX CHILDREN WITH COUGHS

SIR,—I should like to congratulate Dr. Yudkin on his excellent article of Sept. 9. In this age of steroid empiricism one feels impelled to praise someone who has the courage to write "What is the matter with the patient? Why has he come?" To deal with both these questions is the beginning of real medicine. The answer—and I should put the second question first—is and always has been the key to good doctoring.

To listen to the patient tell the story will tell the experienced doctor the diagnosis and will tell him what confirmatory physical signs he is likely to find on examination.

It is this simple understanding of the patient and his situation which solves the greater part of illness because it leads to the correct diagnosis—the nomenclature of which may be difficult to find in any standard work on medicine but may well be found in that enlightened book *Clinical Involvements* by Dr. H. Gardiner-Hill.

The correct diagnosis is so often missed because the patient is swept away to hospital for investigation (a curious term) for many weeks, delighting scores of technicians and special departments, before anyone has taken the trouble to listen to the patient tell his story, in which lies the answer, and then taken the responsibility of making the correct diagnosis.

The return to this sort of real doctoring would improve the health of the people, halve the health bill, and reinstate doctors in their rightful place in society. The time-consuming committees so often rationalising the existence of myriads of departments and beds for the benefit of the doctors' livelihood

would be ended. They would be possibly of interest to the political historians of the future.

Repton, Derby. D. W. S. SHELDON.

LANGUAGE: THE LOST TOOL OF LEARNING

SIR,—Should not the Royal College of Physicians set an example to other eminent examining bodies in medicine by taking heed of the warnings given by Sir George Pickering and Dr. D. M. Jackson? Since we are abusing our language as these writers state, should not a new question be set in all our postgraduate examinations of membership type, to test the ability of candidates in the use of the English language? The requirement would be to translate into acceptable English a piece of prose, devilishly composed in corrupt medical " English ".

Perhaps we should find ourselves unable to judge the answers. We ought at least to find no difficulty in setting the questions.

Hæmatology Department,
Royal Infirmary and Royal Hospital,
Sheffield. H. T. SWAN.

SIR,—The correspondence provoked by Sir George Pickering's recent article encourages me to ask why an experimental animal is so often " sacrificed " rather than just killed. The term conjures up a scene which seems either absurd or downright blasphemous. Is this what the authors intend—or is my imagination too literal?

Welsh National School of Medicine,
Cardiff. D. E. EVANS.

MANAGEMENT EFFICIENCY IN THE HEALTH SERVICE

SIR,—While agreeing with Dr. Searle's diagnosis (Aug. 26) of the ills of the National Health Service I would take issue at almost every point with the treatment he prescribes. A letter is the wrong medium for comments on his whole paper but to touch on one point, there seems to be a basic fallacy in his early premise that the objective of the Service is " the provision of the best care that the nation can afford ".

It is impossible to assess in advance what care the nation can afford; whether it should be more or less than the usual 4% of gross national product depends on varying circumstances. In some years the nation could afford the Ritz, in others a cheap night in a youth hostel, but in any case health should bear no relation to " national product ".

From a service point of view (i.e., disregarding for the moment research and teaching) the objective surely should be the provision of the care (and no more) that the health of the people requires. This means discovering what should be the proper standard of hospital care (or nursing-home care, or family-doctor care) and reaching up or down to it. Materially speaking, to say, as many do, that only the best is good enough for the sick is extravagant nonsense. The best may be nicest but it isn't always necessary.

The average patient having become content with a bed costing him £10 on which to spend his healthy nights does not need one costing £90 when he is sick; a private patient is adequately served with far fewer investigations and visits from his doctor than the public patient gets with the same condition.

The proper standard of care may prove to be a high one but at present no-one knows what it is and no-one is trying to find out. Ought we not to do so?

The Radcliffe Infirmary,
Oxford. E. J. R. BURROUGH.

SIR,—I was not a little astonished to read Mr. Celestin's letter of Sept. 2. I do not know what his experience may have been of hospitals in " pre-National-Health-Service days," but his statement that " we can all think " of people who have " literally bought their way into a hospital " will surprise those of us who, like myself, have been closely concerned with hospital affairs over the past 40 years. If he means what he says, he appears to be under the impression that hospital posts could be bought for money. In a long experience I have never even heard of such a thing being done. It might conceivably have happened in the 18th century, when simony was comparatively respectable, but I find it hard to believe that it has happened within living memory—or even in the last 150 years.

Mr. Celestin's use of the word " crapulence " drove me to my dictionaries, French and English (Bescherelle ainé and the *S.O.E.D.*). The former defines " crapule " as " débauche habituelle, excès dans le boire et le manger "; the latter, under " crapulence ", says " gross intemperance; debauchery ". One wonders why you saw fit to publish a letter whose implications are as false as they are offensive.

London, W.4. MAURICE SHAW.

*** We much regret our inadvertence—ED. L.

THALASSÆMIA MINOR IN A MALTESE VILLAGE

SIR,—In the past twelve years, thalassæmia major (Cooley's anæmia) has been demonstrated in Malta in 12 members of eight families [1] though reports of this condition in only two Maltese families, one in Malta [2] and the other in Tunisia [3] have so far appeared.

That thalassæmia minor was frequent in Malta was observed by one of us (F. V.), in April, 1960, in a search among 2500 healthy schoolchildren. The criterion to determine the presence of thalassæmia was an increased osmotic resistance of the circulating erythrocytes accompanied by morphological microscopical abnormalities of these cells. Because of its simplicity, we used the method devised by Silvestroni and Bianco [4] for their studies on large populations in Italy and Sicily. The children in this survey were attending three large private secondary schools and two Government primary schools. 4% of them had thalassæmia minor.[5]

More recently we extended these tests to a further 3500 children attending Government primary schools in thirteen towns and villages. The previous results were confirmed. The frequency generally varied between 1% and 10%. But in the village of Mellieha, approximately 20% of 260 children tested were found to give positive results. Because of this unexpected finding, almost all the schoolchildren in this village were tested —740 clinically healthy boys and girls in all, from six to twelve years old. These included some 180 sibships each of between 2 and 6 children. Positive results were found in 164 children (22%), and, with the method of Betke and Kleihauer,[6] acid-resistant erythrocytes were found in many of these children. In 33 sibships 2 or more children gave positive results; while in a further 87 sibships normal results were obtained. Among the schoolchildren in the next village (St. Paul's Bay), which is about 3 miles away, the frequency of positives was 5%.

Though a few of the children who gave positive results for thalassæmia minor may have been suffering from a mild degree of iron deficiency, there cannot have been enough of them to alter the results significantly. Thus of all children at Government schools in Malta, only 1% were reported to be anæmic in

1. Cachia, E. Personal communication, 1960.
2. Mooney, F. S. *Arch. Dis. Childh.* 1951, **24**, 231.
3. Roche, J., Derrien, Y., Diacono, G., Roche, M. *Rev. Hémat.* 1953, **8**, 282.
4. Silvestroni, E., Bianco, I. *Amer. J. hum. Genet.* 1949, **1**, 83.
5. Vella, F. Paper read at "Giornate" on the social problem of Cooley's anæmia and microcythæmia. University of Rome, May 14–15, 1961.
6. Betke, K., Kliehauer, E. V. *Blut*, 1958, **5**, 241.

1958, while infestations with intestinal parasites were rare.[7]

Mellieha lies in the northwestern corner of the island. Until recently it was difficult to get to and was probably the most isolated community in Malta. Its population now numbers about 4400; there are 100 live births a year. The infant and child mortality, as elsewhere in Malta, is low: thus, in 1959 and 1960, only 3 children under one year old died and none between the ages of one and ten years. The village can be considered to represent one large family. Thus, of about 60 marriage-partners in the 30 weddings solemnised annually in the past few years, 5 or fewer were not born locally. With this amount of intermarriage, the thalassæmia gene, once introduced, spread rapidly, and probably required only a few generations to reach its present frequency. This suggestion is based on the following facts: (1) The present parish was established in 1844; and (2) no cases of thalassæmia major have yet been noted in this village, even though pædiatricians and other doctors have been looking for it for over a decade.

The possibility that there may be relatively mild thalassæmia major in this village could be checked by extensive family studies of those children found positive for thalassæmia minor. Such studies have not yet been possible.

We wish to thank Prof. J. Galea, Chief Government Medical Officer, Malta, for permission to carry out this investigation; and the Rev. J. Xuereb, parish priest at Mellieha, for information on the village and its history.

Department of Biochemistry, Faculty of Medicine, University of Khartoum, Sudan. F. VELLA.

School Health Service, Department of Health, Valletta, Malta. M. SANT CASSIA.

7. Report on the Health Conditions of the Maltese Islands for 1958. Department of Information, Valletta, 1961.

Obituary

STEPHEN MORTON

M.B. Cantab., M.R.C.P.

THE death of Dr. Morton, pædiatrician in Port Arthur, Ontario, has come as a shock to his friends in this country, who learned from the Press that he had been shot and that the police were searching for his assailant.

Dr. Morton was trained in Cambridge and at the Middlesex Hospital, and qualified in 1944. After holding a medical registrarship at the Park Prewett E.M.S. Hospital at Basingstoke, he specialised in pædiatrics. He was senior resident medical officer at the Queen Elizabeth Hospital for Children in London, and later registrar at this hospital and pædiatric registrar at the Mothers' Hospital, Clapton. Thereafter he went overseas to work in the Hospital for Sick Children in Toronto. He and his wife decided to settle with their children in Canada, and for the last seven years their home has been in Port Arthur, where he was pædiatrician to the general hospital.

A friend and senior colleague at the Queen Elizabeth Hospital for Children writes: "At the Queen's, S. A. Morton was known affectionately as Sam and was warmly liked in the hospital and appreciated both as a skilled and experienced registrar and as a man of integrity, good will, and quiet kindness. He was very popular with his child patients. He always wanted full-time work in the active care of children, and this he achieved in his large and busy pædiatric practice in Port Arthur."

Appointments

BARRITT, D. W., M.D. Lond., M.R.C.P.: consultant physician, department of cardiology and general medicine, Bristol Royal Infirmary.

BENNETT, FIONA M., M.B. Edin., D.OBST., F.R.C.S.E.: consultant ophthalmologist, Aberdeen general hospitals.

COLES, D. R., M.D. Brist., M.R.C.P.: consultant physician, department of physical medicine, Bristol Royal Infirmary.

Notes and News

THE STATE OF FOOD AND AGRICULTURE 1961

THE annual report of the director-general of the Food and Agriculture Organisation[1] reveals a pattern which is now familiar. There is an abundance, often a surplus, of agricultural products in the economically developed parts of the world, side by side with continuing malnutrition and even hunger in many of the less developed countries. In the Far East, outside mainland China, the most populous area in the world and also the worst nourished, a good harvest for the third year in succession has enabled the figure for food production per head to regain its pre-war level. Agricultural development is just keeping pace with the growth of population.

Data for the available food-supplies in different countries show that in Western Europe the situation is good. In Greece, Austria, Yugoslavia, Spain, and Italy, there have been remarkable recoveries from the conditions of 10 years ago, even if in Spain and Italy, with only 2700 calories per head per day, the supply can hardly be described as satisfactory. Only in Portugal, where supplies of meat, eggs, and milk are poor and the calorie value of the national diet is only 2350 per head per day, do there seem to be serious shortages. The curious may like to know that the Irish have more food than any other people in the world—if their figures working out at 3570 calories per head per day are to be trusted. In Latin American countries and in Asia there have been some small improvements in the last decade, notably in India. The only country in which there seems to be relatively less food than 10 years ago is Pakistan. Pakistan used to be significantly better off than India, now India is slightly ahead. There are very few figures for African countries; but in Egypt, where 2650 calories per head per day are now available, there seems to have been a big improvement in supplies.

The cynic can easily make fun at these and many other of the national statistics in this report, especially those for the underdeveloped countries. Nevertheless, F.A.O. are to be congratulated on their perseverance in collecting and presenting clearly such a mass of information each year. Even if the accuracy of individual figures may often be suspect, undoubtedly the general trend of affairs which they represent is correct. It is reports such as this that are the very foundation of the United Nations and the basis for all international assistance.

The report contains two special chapters. One deals at length with agrarian reform since the second world war. As the Director-General states in his foreword, " in no comparable period of history have there been such widespread efforts, affecting so large a proportion of the human race, to establish systems of land tenure better fitted to present needs ". A second chapter deals with the development of agricultural research and education in Asia, Africa, and Latin America. It is a record of progress, but at a rate much slower than is required to reach reasonable standards of living. More money and more and better trained staff are needed to hasten the present inadequate rates of advance.

CENTRAL STERILE SUPPLY

Two useful publications on central sterile supply have lately appeared.

A booklet published by the *Nursing Times*[2] shows how much has already been achieved in this country by a small band of enthusiasts. It falls into two sections—firstly, a balanced summary of present views on all aspects of the subject, and secondly, a series of short accounts of departments that are already established or are being set up, together with a bibliography. This slim volume is concise, well illustrated, and easily read, and those establishing a department in their own hospital or group will find it a valuable source of information.

The second publication, issued by the Ministry of Health,[3] is

1. The State of Food and Agriculture 1961. Rome: F.A.O. Pp. 177. 10*s*. Obtainable from H.M. Stationery Offices.
2. Central Sterile Supply: A *Nursing Times* publication edited by BRIAN WATKIN. London: Macmillan. 1961. Pp. 58. 4*s*. 6*d*.
3. Hospital Building Note no. 13: Central Sterile Supply Department. H.M. Stationery Office. 1961. 1*s*. 6*d*.

intended as a guide to the design of a department at a district general hospital. The supposition is that one department will serve a group of hospitals rather than a single small hospital on the one hand, or part of a region on the other. This arrangement, it is suggested, makes for economy, which is also aided by a proper " work-flow " in the department. The cost of the basic accommodation (including engineering services, equipment, and process machinery) of a department serving 800 or more beds and related outpatient and casualty services is estimated at £36,350. The note, besides discussing the salient features of sterile supply, gives a list of rooms and a description of their contents, and details of engineering services. Much of the prevalent uncertainty about the design of such departments is reflected in the note. A glove preparation room will not be needed if disposable rubber gloves are to be used. Should returned instruments and syringes be disinfected or autoclaved before being washed? Should these items be washed in an ultrasonic or a high-pressure jet washing-machine? Are hypodermic needles to be reprocessed or should they be disposable?

A ROAD SIGN REMOVED

Canvey Island (Essex) Road Safety Committee have followed the suggestion in our leading article of Aug. 26 that distracting road signs should be removed. When they met on Sept. 4 they were told that their board welcoming visitors to the district and giving the number of accidents would have to be put in another place, because the land it is on has been fenced in. A new site was proposed; but Mrs. Gay Edwards (secretary) suggested that the committee might prefer to do what *The Lancet* recommended and withdraw the sign for the present. Agreeing with her suggestion, Councillor Sidney Alterman, chairman of the committee, said: " We can give a national lead on this." It was agreed that the board be taken down and stored for a year. The Post Office are to be asked if the number of road accidents can be displayed *inside* their building.

University of London

Dr. J. P. Quilliam, reader in pharmacology at St. Bartholomew's Hospital Medical College, has been appointed to the chair of pharmacology at the college.

Dr. Quilliam graduated B.SC. honours (physiology) in 1936 and proceeded to the M.SC. (physiology) of the University of London in 1938. He was appointed Sharpey physiological scholar at University College, London, and in 1941 qualified M.B. with honours from University College Hospital. During the late war he was an experimental officer at the Chemical Warfare Experimental Station, and in 1943 he joined the medical branch of the Royal Air Force. In 1946 he was appointed lecturer at King's College and two years later part-time lecturer in pharmacology at St. Bartholomew's Hospital Medical College. In 1949 he was fellow in residence at Johns Hopkins University. He was appointed senior lecturer in charge of the new department of pharmacology at St. Bartholomew's Hospital Medical College in 1956 and reader there in 1958. He is a member of the General Optical Council and an editor of the *British Journal of Pharmacology and Chemotherapy*. His research interest has centred on neuromuscular and ganglionic transmission and its modification by centrally acting agents.

The degree of M.D. has been awarded to R. E. Cotton and C. J. Edmonds.

University of Dublin

At a special commencement held at Trinity College on Sept. 5 to mark the congresses of the International Society of Surgery and the International Cardiovascular Society the honorary degree of M.CH. was conferred on Prof. Paul Martin (Brussels), Prof. C. G. Rob (New York), Prof. João Affonso Cid Dos Santos (Lisbon), and Dr. Pierre Wertheimer (Lyons).

University of Oslo

On Sept. 4 Sir Wilfred Le Gros Clark and Prof. E. J. King received honorary doctorates.

Hospital Patient—Person or Case?

A conference on this subject is to be held by the Royal College of Nursing from Oct. 30 to Nov. 2 at Church House, Westminster, London, S.W.1. Application forms may be had from the conference secretary at the college, Henrietta Place, London, W.1. The closing date for applications is Oct. 4.

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the faculty on Sept. 4, with Dr. J. H. Wright, the president, in the chair, the following were admitted to the fellowship:

Sabri Ismail Ahmed, Fazal Ali Akbar, Majeed Jerjees Al-Shamma'a, J. R. Anderson, Cyril Bainbridge, Cyril Cohen, Manohar Singh Grewal, Zuhair Abdulla Kassir, James Laurie, L. G. C. Martin, Narayan Waman Moholkar, J. J. Morrow, Parthasarathy Narasimhan, T. G. J. Phillips, Wai-on Phoon, D. A. Pitkeathly, Gopal Rabindranath, Manohar Rao, Mohammad Sharif, Malik Ali Sheikh, R. W. Strachan, Panchanan Tiwary, Jagadish Tripathy, *qua* physician; Fawzy Mostafa Abdel-Kader, R. W. Bailie, Soo Huat Choo, Mary S. Christian, J. H. Grant, I. B. Hall, R. G. Henderson, J. A. Imrie, Dilip Kumar Mukherjea, G. D. Smellie, J. S. S. Stewart, I. C. Whyte, *qua* surgeon.

Institute of Obstetrics and Gynæcology

On Tuesday, Sept. 19, at 3 P.M., at Hammersmith Hospital, Ducane Road, London, W.12, Prof. D. B. Stewart, of the University College of the West Indies, will speak on the infectious granulomata of the female genital tract. Admission tickets may be had from the secretary of the institute, Chelsea Hospital for Women, Dovehouse Street, S.W.3.

Institute of Diseases of the Chest

Clinical demonstrations will be arranged by Dr. Joseph Smart at the Institute, Fulham Road, London, S.W.3, on Fridays, at 5 P.M., from Oct. 6 to Dec. 15.

Institute of Neurology

On Thursday, Sept. 21, at 3.30 P.M., Prof. Elizabeth Roboz-Einstein, of the University of California, will give a lecture on the biochemical approach to multiple sclerosis and allergic encephalomyelitis, and at 5.30 P.M. Dr. G. von Békésy, of Harvard University, a lecture on lateral inhibition in the skin, the ear, and the eye. Both lectures will be given at the Institute, Queen Square, London, W.C.1.

Medical Protection Society

The annual general meeting will be held at the society's offices, 50, Hallam Street, London, W.1, on Wednesday, Oct. 4, at 3 P.M.

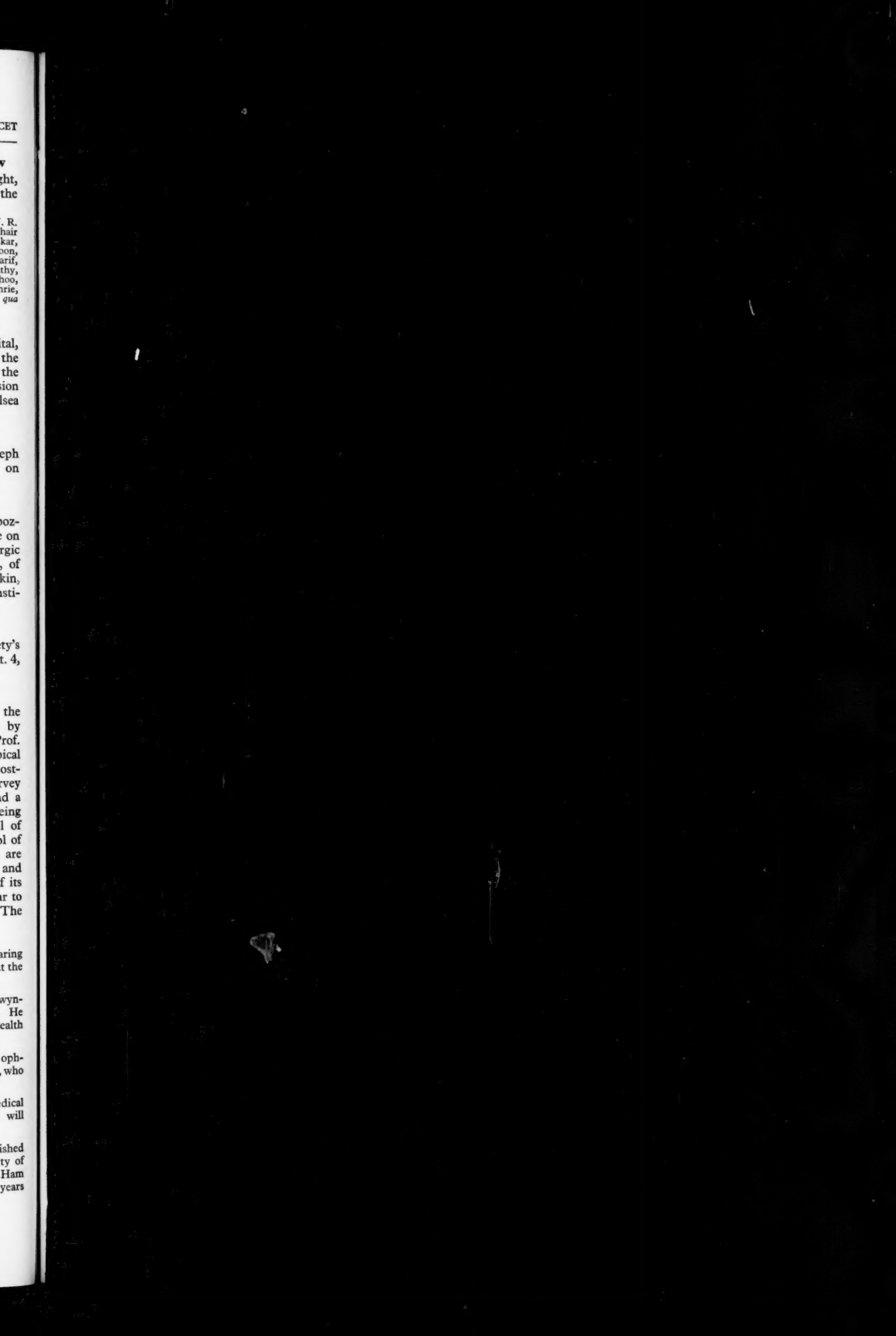
Tanganyika's Medical Needs

As a basis for its future development of health services, the Tanganyika Government has asked for a survey report by Prof. R. M. Titmuss (London School of Economics), Prof. George Macdonald (London School of Hygiene and Tropical Medicine), and Dr. Arthur W. Williams, director of post-graduate medical services at Oxford University. This survey will be set up by the African Research Foundation, and a preliminary study of the Territory's health services is being made by Dr. Christopher Wood of the London School of Hygiene and Dr. Brian Abel-Smith of the London School of Economics. Professor Macdonald and Dr. Williams are already very familiar with circumstances in East Africa, and their team will operate mainly in London, though one of its members may go to Tanganyika about the end of this year to gather any further information that may be needed. The report is expected early in 1962.

The Duke of Devonshire will give the inaugural address to Charing Cross Hospital Medical School on Thursday, Oct. 12, at 3 P.M. at the Senate House, London, W.C.1.

On the invitation of the President of Ghana, Sir Selwyn Selwyn-Clarke will be visiting that country in October and November. He is to review the problems that may arise in carrying out the health programme and to offer constructive criticisms.

Mr. F. W. Law has been appointed honorary consultant in ophthalmology to the Army in succession to Sir Stewart Duke-Elder, who has retired.

On Tuesday, Sept. 19, at 5 P.M., at the Royal Army Medical College, Millbank, London, S.W.1, Prof. M. L. Rosenheim will speak on investigation of hypertension.

A scholarship in memory of Mr. S. I. Levy has been established by his widow at the Medical School of the Hebrew University of Jerusalem. Mr. Levy was for many years surgeon to the East Ham Hospital and to the Westminster Hospital, and for about thirty years senior surgeon to the London Jewish Hospital.